

1 way by each study investigator. This  
2 precludes any ability to pool results from the  
3 different study sites and investigators.

4 I would like to take a few moments  
5 now to respond to the assertions that Cardima  
6 has made and has reported about its study and  
7 results. Cardima claims that episodes of  
8 paroxysmal atrial fibrillation occur at a  
9 consistent, periodic, or predictable manner on  
10 a monthly basis.

11 While the agency would agree that  
12 some patients experience symptoms at a regular  
13 frequency, the disease of paroxysmal atrial  
14 fibrillation is highly heterogeneous. It is  
15 very possible, if not likely, for patients to  
16 experience a single or cluster of episodes,  
17 then remain without symptoms for some time,  
18 even for the one month, and then have a  
19 recurrence of AF episodes.

20 Cardima does not believe that the  
21 study had confounding factors that would  
22 contribute to the inability to clearly  
23 delineate the true effectiveness of the device  
24 system. FDA disagrees with this assumption.

25 One example of this factor that

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1 occurred in the study is pacemaker implants.  
2 It is very possible that patients who receive  
3 pacemaker implants also change their  
4 perception of symptoms associated with AF.

5 In other words, it is possible that  
6 a patient may have had an improvement in AF  
7 symptoms due to the pacemaker and not due to  
8 the treatment with the ablation catheters.  
9 Thus, this patient, who otherwise might count  
10 as a study failure, would now count as a study  
11 success.

12 FDA expected that Cardima would  
13 manage its study as designed. FDA did not  
14 anticipate that the study would suffer from  
15 flaws in data collection at baseline, during  
16 the ablation procedure, and during the  
17 follow-up evaluation periods.

18 At a very simple level, FDA did  
19 approve a valid study design by the sponsor  
20 and expected Cardima to collect the important  
21 safety and effectiveness data per its own  
22 protocols.

23 The Cardima study was designed by  
24 the sponsor and approved by FDA to evaluate  
25 its catheter ablation system consisting of

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1 both the Revelation Tx and NavAblator  
2 catheters in the formation of a composite  
3 lesion set for the treatment of atrial  
4 fibrillation. The study was neither designed  
5 nor intended to tease out specific effects of  
6 only one catheter or of only specific lesions.

7           You have heard from the sponsor  
8 this morning with respect to their quality of  
9 life results. The QOL information in the  
10 study was intended and designed as a secondary  
11 endpoint and not as a primary measure. The  
12 quality of life results may be interesting and  
13 potentially suggest an improvement in patient  
14 outcomes, even in an unblinded study with the  
15 potential for placebo effect to impact study  
16 results.

17           However, in the absence of our  
18 ability to confirm to what extent the device  
19 system was used in the ablation procedure,  
20 this fact, coupled with the unblinded study  
21 and its confounding factors completely  
22 undermine our ability to draw any conclusions  
23 with respect to this endpoint. Moreover, any  
24 conclusions that could be drawn cannot  
25 overcome the lack of acute and chronic

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1 effectiveness data on the device system.

2 Finally, you have heard today  
3 literature references in support of Cardima's  
4 application. However, the literature  
5 describes a wide set of treatments, patient  
6 conditions, and data collection methodologies.

7 As a result, it is not possible to  
8 extrapolate these results and findings to the  
9 Cardima trial results. The Cardima data need  
10 to stand on their own. And this literature  
11 may not serve as a substitute for data  
12 specifically required on the Cardima device  
13 system.

14 FDA has spent a considerable amount  
15 of time and resources in reviewing the Cardima  
16 PMA over the past four years. The consistent  
17 message communicated by FDA over this time has  
18 been the same.

19 Existing data submitted by Cardima  
20 were so fundamentally incomplete that it was  
21 not possible to reach any conclusion regarding  
22 safety and effectiveness. New safety and  
23 effectiveness data are needed in order to  
24 permit this evaluation.

25 This message was first communicated

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1 by the seven members of the Circulatory  
2 Systems Devices Panel, who, in May 2003,  
3 recommended that the device system be found  
4 not approvable. The message was then  
5 communicated by FDA in the first not  
6 approvable letter issued later that year.

7 As discussed by Dr. Ewing in her  
8 presentation earlier this morning, amendment  
9 six involved the combination of additional  
10 phase 3 data with previously reviewed phase 3  
11 data that was originally reviewed in the  
12 original PMA.

13 Amendment six had no impact on the  
14 overall conclusion that we made about the  
15 Cardima ablation system. As a result, the  
16 message was again communicated by FDA in the  
17 second not approvable letter sent in response  
18 to amendment six.

19 In the subsequent meetings held  
20 with Cardima, FDA has clearly and consistently  
21 communicated that the fundamental deficiencies  
22 with respect to the collection of baseline,  
23 procedural, and follow-up safety and  
24 effectiveness data left the agency with no  
25 option but to conclude that new clinical data

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1 are required.

2 You will have an opportunity to  
3 discuss the merits of the application and to  
4 decide whether FDA's decision to not approve  
5 the PMA was correct. In order for FDA to have  
6 decided that the Cardima PMA be approved, with  
7 or without conditions, FDA needed to determine  
8 that a reasonable assurance of safety and  
9 effectiveness was indeed demonstrated.  
10 Unfortunately, the problems with the  
11 submission prevented the FDA, along with the  
12 expert advisory panel, from reaching this  
13 conclusion.

14 As a result, because FDA determined  
15 that new clinical data were needed to evaluate  
16 the device safety and effectiveness, the only  
17 option that FDA was left with was to decide  
18 that the PMA be found not approvable.

19 FDA remains committed in working  
20 with the sponsor to help them design and  
21 implement a subsequent study that will permit  
22 an evaluation of the safety and effectiveness  
23 profile of the device system.

24 In your deliberations later today,  
25 you will also be asked to determine whether

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1 you believe that reasonable assurance of  
2 safety and effectiveness was shown based on  
3 the sponsor's data.

4 If you believe, as with FDA, that  
5 additional clinical data are needed to  
6 evaluate device safety and effectiveness, then  
7 a vote consistent with this determination  
8 would be to vote "not approvable."

9 We look forward to the ensuing  
10 discussion regarding your interpretation of  
11 the data and FDA's prior decision. We welcome  
12 any questions you may have for us. And on  
13 behalf of the entire FDA review team, I would  
14 like to thank you for your consideration of  
15 this application.

16 Thank you.

17 CHAIRPERSON RAMSEY: Thank you for  
18 that presentation.

19 We now have a second --

20 DR. ZUCKERMAN: Excuse me, Dr.  
21 Ramsey. Do we have additional time?

22 CHAIRPERSON RAMSEY: Yes if you  
23 would like to take some. Sorry. I didn't  
24 mean to cut you off. You are certainly  
25 welcome to take your time. So there are about

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1 four minutes left.

2 DR. ZUCKERMAN: No problem, sir. I  
3 just have a few short comments that I would  
4 like to continue along Dr. Elias Mallis'  
5 lines. Number one, Dr. Cher and Dr. Li have  
6 just kind of given you the tip of the iceberg  
7 with respect to the interesting statistical  
8 modeling that can be done in this area.

9 I would welcome the panel in the  
10 afternoon to further question our statistical  
11 consultants because Dr. Cher's interpretation  
12 of the results that you get with a more  
13 elaborate and refined statistical model I  
14 don't think are correct. And they actually  
15 support the FDA position, number one.

16 Number two, I would again just go  
17 back to the fundamental principles of this  
18 dispute. Again, you have heard about a 1998  
19 panel meeting. Both the agency and the  
20 sponsor agree that the trial design talked  
21 about at that panel meeting was a relevant  
22 one.

23 And I think what is being missed  
24 perhaps by the sponsor is that during that  
25 discussion, the many electrophysiologists who

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1 took part in that discussion really indicated  
2 that if you were going to use a one-armed  
3 trial, that the devil is really in the  
4 details.

5 And that is why the agency has  
6 consistently indicated that the acute  
7 procedural endpoint evaluation is an important  
8 one. From a practical perspective, how does  
9 the electrophysiologist know how to get out,  
10 know when to get out of the EP lab?

11 We will be more than glad to show  
12 you this afternoon when you look at per-site  
13 effectiveness results. Whether you use the  
14 Cardima evaluation system or the FDA system,  
15 there is a factor of three difference. This  
16 is due to the fact that we really don't know  
17 what happened acutely with this catheter the  
18 same way, chronically, we need to get a better  
19 assessment of what are the chronic  
20 effectiveness results in order to see if this  
21 is a system and a device that is an important  
22 part of the armamentarium.

23 Where we do agree with the sponsor  
24 and perhaps everyone in the room is that  
25 atrial fibrillation is an important public

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1 health problem. We just need to see the data  
2 in front of us to decide whether we have an  
3 important new device system to treat this  
4 complex problem.

5 Thank you.

6 CHAIRPERSON RAMSEY: Thank you.  
7 There are still maybe a few more seconds.

8 (Laughter.)

9 CHAIRPERSON RAMSEY: And I would be  
10 happy to yield them to you if you have any  
11 other comments. Otherwise we will move to the  
12 second open portion of this hearing. Okay?

13 (No response.)

14 CHAIRPERSON RAMSEY: Okay. So we  
15 will now proceed to the second open portion  
16 hearing of the meeting. Are there any  
17 individuals who wish to speak today? There is  
18 one? Okay. Two? Okay.

19 Let me read a statement first. And  
20 then I will invite you up to speak. "Both the  
21 Food and Drug Administration and the public  
22 believe in a transparent process for  
23 information-gathering and decision-making. To  
24 ensure such transparency at the open public  
25 hearing session of the Advisory Committee

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1 meeting, FDA believes that it is important to  
2 understand the context of an individual's  
3 presentation.

4 "For this reason, FDA encourages  
5 the public hearing speakers at the beginning  
6 of the oral or written statement to advise the  
7 Committee of any financial relationship you  
8 may have with the FDA; the sponsor; its  
9 product; and, if known, its direct  
10 competitors.

11 "So, for example, this financial  
12 information may include the sponsor's payment  
13 of your travel, lodging, or other expenses in  
14 connection with attending the meeting.

15 "Likewise, FDA encourages you, at  
16 the beginning of your statement, to advise the  
17 Committee if you do not have any such  
18 financial relationships. If you choose not to  
19 address this issue of financial relationships  
20 at the beginning of the statement, it does not  
21 preclude you from speaking."

22 I would ask that you keep the  
23 comments to ten minutes if at all possible so  
24 that we may move forward with the discussion  
25 section in a timely fashion.

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1 I have on my list here that the  
2 first speaker is Dr. Jon E. Block. Dr. Block?

3 While they are getting set up, would you like  
4 to state your relationships?

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6 DR. BLOCK: Certainly. My name is  
7 Jon Block. I am an independent clinical  
8 trials consultant. I am being remunerated for  
9 this trip by the sponsor. And I own stock in  
10 the company, which I purchased publicly over  
11 two years ago.

12 CHAIRPERSON RAMSEY: Just again  
13 procedurally, so I have ten minutes. I will  
14 give you a warning at five and at one.

15 DR. BLOCK: Very well.

16 CHAIRPERSON RAMSEY: Okay.

17 DR. BLOCK: Thank you.

18 CHAIRPERSON RAMSEY: But I won't  
19 penalize you until the slides come up. Go  
20 ahead.

21 DR. BLOCK: Thank you,  
22 distinguished members of the panel.

23 I would like to talk to you today a  
24 little bit about putting right atrial ablation  
25 into perspective, particularly with respect to

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1 the Maze procedure, as well as talk about  
2 other non-specific study effects and how they  
3 might have affected these data in some senses.

4 Next slide, please. I was retained  
5 by the sponsor after the first panel meeting  
6 to work on two particular publication efforts.

7 One was a synthesis of the world literature  
8 on right atrial catheter ablation -- we  
9 published that in 2004 -- and, secondly, to  
10 write up the clinical trial results that are  
11 the discussion today. And we published those  
12 in 2005. I will refer to that paper as  
13 Kocheril 2005. That's essentially the same  
14 data that we are talking about today. And I  
15 must remind you that that passed peer review  
16 muster for independent peer reviewers.

17 I use the term "clinical success"  
18 throughout this presentation. I'm referring  
19 to a clinical- relevant reduction in or  
20 elimination of AF episodes with or without the  
21 concurrent use of anti-arrhythmic drugs. I  
22 don't think there's any debate or certainly  
23 little debate about the therapeutic  
24 effectiveness of the surgical Maze procedure.

25 Early in the 1990s and then going

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1 into the early 2000s, Jim Cox at Washington  
2 University in St. Louis published a number of  
3 studies on the Maze procedure. His results,  
4 obviously, as you can see, are quite  
5 impressive with respect to clinical success in  
6 excess of 95 percent with the addition of  
7 anti-arrhythmic drugs in some cases.

8 But, as with all surgical  
9 procedures, when other people begin to start  
10 doing the procedure, the success rates begin  
11 to go down. And, as other people started  
12 doing the surgical Maze procedure, their  
13 success became less potent in some senses.

14 We have a median success rate over  
15 a number of studies using both cut and sew as  
16 well as RF ablation in an open surgical  
17 setting of about 85 percent, which is at least  
18 10 percentage points less than what was  
19 achieved in the Cox experience.

20 And, as Dr. Saksena has pointed out  
21 earlier, by the mid '90s, there was an exodus  
22 away from bi-atrial procedures as generally  
23 over to the left atrium due to the discovery  
24 of triggers in the left atrium.

25 So, even in the surgical setting, a

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1 number of authors began to move over to the  
2 left atrium and began to do open surgical  
3 procedures just on the left side. Their  
4 success rate on a median average is about 84  
5 percent.

6 What is interesting here as well is  
7 that much of this success was achieved with  
8 the continued addition of anti-arrhythmic  
9 drugs in addition to surgery. So surgery in  
10 and of itself is not necessarily curative.  
11 Many of these patients remain on  
12 anti-arrhythmic drugs for pretty much an  
13 indefinite period of time.

14 As I indicated earlier, I  
15 synthesized the literature with respect to  
16 right atrial catheter ablation. These are all  
17 of the studies that have been published to  
18 date on right atrial catheter ablation. The  
19 median success rate is approximately 58  
20 percent.

21 Coincidentally, that success rate  
22 is exactly the same success rate as we found  
23 in the Kocheril 2005 paper, which, as I said,  
24 is the same success rate that you're looking  
25 at today.

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1 I want to point out another  
2 interesting thing about this slide. And that  
3 is that one group in Japan; Kosakai, in  
4 particular, performed a right-only open Maze  
5 procedure. And he achieved a success rate of  
6 approximately 50 percent, nowhere near the 90  
7 or 95 percent that was achieved with Cox's  
8 original bi-atrial Maze procedure.

9 So, stacking up these right atrial  
10 procedures, both open surgical, the Kocheril  
11 data, and the median of all the published  
12 data, they're pretty much all in the same  
13 ballpark. So in terms of whether these are  
14 realistic data or whether they are illusory,  
15 they seem to be certainly what other people  
16 have reported before and certainly in keeping  
17 with a right-only Maze procedure.

18 Comparing all of these medians over  
19 different procedures, obviously the Cox data,  
20 the most dramatic and impressive, going down  
21 from there, and then putting both the Kocheril  
22 2005 paper and the median of all the RA  
23 catheter ablation studies in perspective, we  
24 see that, in context, these numbers actually  
25 look quite realistic.

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1                   This is an informative slide. Most  
2 surgeons have now moved away from the cut and  
3 sew procedure of Cox. It's an arduous, long,  
4 complex procedure. They have now moved to  
5 other alternative types of Maze procedures.

6                   This is a recent systematic review  
7 of different types of Maze procedures compared  
8 to the cut and sew Maze using both alternative  
9 energy sources, such as cryoablation,  
10 radiofrequency ablation, and so forth. And so  
11 you see that the success rates are pretty  
12 similar.

13                   CHAIRPERSON RAMSEY: Just under  
14 five.

15                   DR. BLOCK: Thank you.

16                   Now with regard to the placebo  
17 effect and how it may have affected these  
18 findings because this obviously is a single  
19 arm study, there's been a number of  
20 international -- the international CONSORT  
21 Committee, for example, found that with  
22 respect to placebo, particularly, the most  
23 subjective outcomes are the ones that we  
24 should be most concerned about, particularly  
25 with pain. When we are looking at harder

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1 outcomes, there's really little room for bias,  
2 as they point out.

3 In here, in terms of soft outcomes  
4 that might be subjected to placebo effect, you  
5 might have something like pain severity, on  
6 the far end hard outcomes, something like bone  
7 marrow density, for example.

8 From my perspective, I would see  
9 TTM recordings of AF episodes as being sort of  
10 intermediate in that perspective, certainly  
11 not a soft outcome, maybe not a hard outcome  
12 either, but somewhere in the middle.

13 One might ask, how could we  
14 possibly estimate what that placebo effect  
15 might be. Well, we have accepted the Maze  
16 procedure a priori as being therapeutic in the  
17 management of AF, but it wasn't until 2002 or  
18 2003 that people started actually doing  
19 randomized controlled trials of the Maze  
20 procedure, even though it was long accepted as  
21 a therapeutic management.

22 These are three randomized  
23 controlled trials of the open Maze procedure  
24 with mitral valve replacement versus mitral  
25 valve alone. And we see control group success

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1 rates on the order of about 25 percent.

2 Now, you say, "Well, how does  
3 mitral valve surgery alone possibly reduce AF  
4 burden#. Well, I looked at about four studies  
5 that have looked at mitral valve surgery alone  
6 and how they might affect AF burden. And it's  
7 about 20 percent on average or so depending on  
8 the patient population.

9 So that jibes somewhat with this 25  
10 percent success rate in this control group.  
11 Even in the worst case analysis, if all of  
12 that 25 percent were considered placebo, how  
13 does it stack up against the Kocheril data?

14 Well, I did two calculations. And  
15 this gets to the issue that was raised earlier  
16 about, well, how would we stack up against the  
17 placebo effect?

18 The Kocheril 2005 data compared to  
19 a 25 percent success rate is significant at  
20 the 0002 level. Now, the hypothesis here  
21 depends on equal sample sizes, of course, in  
22 the two groups. Let's take out 12 patients  
23 because they had new AADs added. We're down  
24 to 44 percent, still significantly better than  
25 a hypothetical 25 percent control group at the

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1 .015 level. That's Fisher's exact test for  
2 both of those calculations.

3 Is the 58 percent success rate  
4 because it's a single arm study inflated? Two  
5 systematic reviews published in the New  
6 England Journal of Medicine would certainly  
7 indicate that observational trials do not  
8 inflate treatment effects compared to  
9 randomized control trials. So we think or  
10 certainly I would believe that the 58 percent  
11 success rate is real.

12 Now, in conclusion, we see that  
13 this is a procedurally very easy technique.  
14 It has an excellent safety profile. With  
15 respect to the Maze procedure, we have moved  
16 from open, cut and sew to alternative ways of  
17 doing the Maze procedure to minimally invasive  
18 Maze to catheter ablation.

19 CHAIRPERSON RAMSEY: One minute.

20 DR. BLOCK: The findings seem to be  
21 reasonable and clinically satisfactory when  
22 you compare them to both open Maze procedure,  
23 to previous studies of catheter ablation and  
24 it represents a conservative, prudent first  
25 step into this area.

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1           If you were to say 50 to 60 percent  
2 of the patients would be obviated, another  
3 procedure after this if you were to look at  
4 these data, I believe that the issues raised  
5 by the regulators are unreasonable,  
6 particularly in light of all of the scientific  
7 evidence that has been raised by the sponsor  
8 and none of it by the regulators.

9           Those of us that are clinical  
10 researchers depend on the peer-reviewed  
11 literature. We do not depend on speculation.

12         So I feel catheter ablation has finally  
13 reached prime time.

14           Thank you very much.

15           CHAIRPERSON RAMSEY: Thank you for  
16 that presentation.

17           I'm going to ask the second speaker  
18 to come up and give his presentation. And  
19 then we'll have a brief moment for the panel  
20 to ask questions of either speaker.

21           So Dr. Jaswinder Gill? I'm sorry  
22 if I have mispronounced that. Dr. Gill,  
23 perhaps while they are setting up, you could  
24 just, if you choose, state your relationships  
25 with the FDA or the sponsor.

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1 DR. GILL: My name is Jaswinder  
2 Gill. I work in London at an institution  
3 called Guy#s and St Thomas#, which is a large  
4 university center. And if any of you come  
5 down to London, it's just straight in front of  
6 Big Ben. So you can see where we are.

7 I work with Cardima products  
8 because I am interested in the technology. I  
9 am not funded for any studies. I am not  
10 sponsored for any of the studies by Cardima,  
11 though I hope they will eventually pay me some  
12 money for coming to this meeting.

13 (Laughter.)

14 DR. GILL: Cardima products are  
15 actually licensed in Europe. And they are  
16 available to be used because they have CE  
17 marking. We in Britain are fairly  
18 conservative, and we use them for ablation,  
19 though I've always said, "If you give it to a  
20 Frenchman, I don't know what he would do with  
21 it."

22 I am going to talk a little of our  
23 experience using the Cardima system. I want  
24 to just go back to AF ablation. We know that,  
25 for example, with paroxysmal atrial

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1 fibrillation, isolation of the pulmonary vein,  
2 this is an important issue, but there are many  
3 extra pulmonary triggers and rotors, as Dr.  
4 Saksena has mentioned, which originate from  
5 the right side, including the Christa, the  
6 coronary sinus, and the SVC.

7           In persistent atrial fibrillation,  
8 simple pulmonary ablation is very rarely  
9 successful. And we are more likely to need  
10 extensive ablation over the left atrium and  
11 possibly the right atrium.

12           I think that we have got quite a  
13 lot to learn from the surgeons. We  
14 electrophysiologists don't like learning from  
15 the surgeons, but we have a lot to learn from  
16 Cox's work, where he showed that ablating the  
17 left and the right atrium could achieve quite  
18 remarkable success rates in people with badly  
19 diseased areas, atria, and the maintenance of  
20 sinus rhythm in these patients. In fact,  
21 about 97 percent of patients were in sinus  
22 rhythm following his procedure and 84 percent  
23 in sinus rhythm at 3 months.

24           This procedure does have a  
25 substantial morbidity and mortality. And we

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1 as electrophysiologists have, therefore, been  
2 trying to reproduce this in a minimally  
3 invasive way, which allows us to actually  
4 achieve a safer and easier procedure to do,  
5 which carries less morbidity to these  
6 patients.

7 I personally have been ablating  
8 atrial fibrillation since around 2000 and  
9 started initially with the main premise that  
10 in the RA Maze left atrium, it started with  
11 pulmonary vein isolation. The question arises  
12 as to what to do with those patients who recur  
13 after pulmonary vein isolation. Do we go in  
14 there and repeat the pulmonary vein isolation?

15 Do we pulmonary vein isolate with left atrial  
16 lines? Do we pulmonary vein isolate them with  
17 the addition of a right atrial Maze?

18 In the old days, I was a little  
19 conservative. I did not want to go into the  
20 left atrium and do extensive ablation. So I  
21 elected to go to PV isolation with a right  
22 atrial Maze doing a procedure which is very  
23 similar to that described by Dr. Kocheril.

24 The initial catheters we had for  
25 doing this were the drag and burn technique

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1 very much, which is being employed in the  
2 atrium, but with the advent of the specialized  
3 linear ablating catheters, I was very keen to  
4 try and use these.

5 In order to get a decent ablation  
6 with them, there are some necessary conditions  
7 which have to be fulfilled. Firstly, you have  
8 to be able to localize where the catheter is,  
9 to make sure it lies in the right place. You  
10 have to have an ability to provide continuous  
11 burns and an ability to assess the  
12 completeness of the line.

13 We have used various technologies,  
14 including Navix; Ensite; intracardiac  
15 echocardiography; and more recently XMR, which  
16 is MRI-related, ways of assessing where the  
17 catheters are. And all of these technologies  
18 work reasonably well without problems.

19 And in terms of assessing the  
20 completeness of the line, we have basically  
21 gone for the use of the Ensite. This view  
22 shows you some radiographs of the catheter in  
23 place along the anterior wall and along the  
24 septum, showing the ablation being done. And  
25 you can see that most of these, you can

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1 actually do the whole line with one or two  
2 applications with the caster being slid into  
3 one or two positions.

4 I was quite interested in the  
5 discussion from the FDA, where one focuses on  
6 the diminution of the local electrogram or the  
7 appearance of split potentials or fractionated  
8 potentials.

9 But these are only surrogates,  
10 after all. What really will show you whether  
11 there is a line of block is either pacing on  
12 one side of the line with timing and  
13 propagation analysis or the use of 3D mapping  
14 techniques to look at the propagational  
15 wavefront. I think the data which we have  
16 which uses the Ensite is much more useful.

17 This is an example of an  
18 intracardiac 3D reconstruction using ICE  
19 showing the catheter along the anterior wall.

20 And you can see that it goes and fits very  
21 comfortably. And when we looked with Ensite,  
22 we could see that there was a small gap in the  
23 line which we had created.

24 And these are some examples of --  
25 we have now done 32 patients with Ensite

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1 showing examples of the wavefront pacing from  
2 either side of the line bouncing off this line  
3 of block and going across to the rest of the  
4 atrium, having not crossed the line.

5 These line applications have been  
6 so successful that we have stopped using  
7 Ensite because Ensite costs us about two and a  
8 half thousand pounds every time we open up the  
9 balloon.

10 And we found that usually if there  
11 are gaps, they are almost always where the  
12 overlap occurs when you slide the catheter  
13 from one site to another. And if you have a  
14 decent overlap, then you don't --

15 CHAIRPERSON RAMSEY: Five minutes.

16 DR. GILL: Thank you.

17 These are views of the septal line.

18 And here you have a view, which I think Dr.  
19 Kocheril also showed, where the two lines are  
20 on either side in the posterior view. And you  
21 can see that the activation sequence is  
22 trapped between those two lines.

23 We have looked at our data of the  
24 performance of a right atrial Maze in  
25 association with pulmonary vein isolation. We

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1 had twenty-five patients, mostly males. And  
2 the age group is fairly typical.

3 These all had a lot of atrial  
4 fibrillation over a long period of time. And  
5 many of these were persistent atrial  
6 fibrillations, rather than paroxysmal atrial  
7 fibrillations. And they had mild degrees of  
8 atrial and left ventricular disease.

9 We took these patients after they  
10 had had their pulmonary vein isolation. And  
11 they had failed pulmonary vein isolation. In  
12 other words, these patients all had failed a  
13 previous pulmonary vein isolation procedure.  
14 Many of these had had cardioversion before.  
15 And they had tried a number of anti-arrhythmic  
16 drugs.

17 In these patients, we went on to  
18 re-look at the pulmonary veins. Some of these  
19 pulmonary veins needed some touching up. But  
20 the main procedure was there to put in two  
21 right atrial lines, one across the anterior  
22 wall and one across the septum. And here you  
23 can see the duration of the procedure, which  
24 is around three, three and a half hours, to  
25 four hours in totality.

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1           Now, the important thing is that  
2 out of these very symptomatic patients, we  
3 follow these patients long-term. They all  
4 come back to my clinic. And 13 patients  
5 maintained sinus rhythm long-term; whereas,  
6 previously they had all been fibrillating away  
7 in some form or another.

8           And if you look at the number of  
9 drugs which these patients had tried in the  
10 previous year versus the following year, you  
11 can see that the red dots are much smaller  
12 than the blue columns. And these patients  
13 required less drugs.

14           Another fairly hard end point is  
15 the number of DC cardioversions these patients  
16 required in the year prior to the ablation and  
17 following the ablation. You can see there is  
18 a very considerable reduction in the number of  
19 DC cardioversions which were required in these  
20 patients.

21           Now, any invasive procedure carries  
22 complications. And the possible complications  
23 here are phrenic nerve damage, AV nodal  
24 damage, embolization, and perforation.

25           Of these patients, only one patient

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1 developed tamponade. And it was managed by  
2 pericardial drainage. There were no cases of  
3 AV nodal damage, no strokes or TIAs. And,  
4 interestingly, we did not see atypical atrial  
5 flutters, which are seen when you leave gaps  
6 in this line. And so my belief is that the  
7 right atrial Maze procedure is a safe and  
8 effective procedure.

9 To conclude, linear ablating  
10 technology I believe offers us a significant  
11 advance on what is available. And this is for  
12 a number of reasons. Firstly, the catheter is  
13 relatively easy to place. If you are giving  
14 it to even a first-time electrophysiologist,  
15 he will be able to get it into place  
16 relatively easily.

17 There is lack of gaps when you  
18 apply that line. And with the newer  
19 technologies where you can apply multiple  
20 poles, at the same time the procedure is  
21 considerably more rapid than going one pole at  
22 a time. So it allows us the ability to put  
23 linear lines in set positions without leaving  
24 gaps.

25 And the data which we have suggest

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1 that the procedure is safe and without major  
2 complications. And I think for us to actually  
3 not be able to advance this procedure forward  
4 and improve our patients would be a great  
5 travesty.

6 Thank you very much.

7 CHAIRPERSON RAMSEY: Thank you, Dr.  
8 Gill, for that presentation.

9 We now have a few moments. If the  
10 panel wishes to ask questions of our speakers,  
11 the speakers who just presented, we can do  
12 that. I would ask that those questions relate  
13 only to scientific issues, not to financial  
14 relationships, although I don't think anyone  
15 really planned to do that.

16 If anyone has any questions for the  
17 speakers, now is the time to ask it, the two  
18 public speakers.

19 MEMBER SLOTWINER: Maybe I could  
20 just ask Dr. Gill a question. Thank you. Now  
21 that you don't use the Ensite balloon to  
22 confirm a line of block, what is your  
23 endpoint?

24 DR. GILL: We place the lesions  
25 there, move the catheter because on the Navix

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1 system, you can actually mark where the  
2 catheter is in terms of your position. We  
3 place it into position to give us an anterior  
4 line and a septal line and come out.

5 MEMBER SLOTTWINER: Is there any way  
6 to confirm? Do you measure electrogram  
7 amplitude?

8 DR. GILL: We have done. We don't  
9 find it a desperately useful measure. If you  
10 have the quite clear appearance of split  
11 potentials, that's a very useful measure, I  
12 think. Split potentials in general tell you  
13 that you've got two different activation  
14 sequences on either side of the line.

15 But we have seen conduction block  
16 occur in people who have diminution of the  
17 potential at the time when you apply and those  
18 people who don't have diminution of the  
19 potential when you apply.

20 But actually measuring the  
21 propagational wavefront or pacing on either  
22 side of the line and measuring your timing  
23 intervals I think is really the only way to  
24 really tell whether you have actually got a  
25 line of block or not.

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1 MEMBER SLOTWINER: Thank you.

2 CHAIRPERSON RAMSEY: Yes. Okay.

3 One other question. Sure.

4 MEMBER SACKNER-BERNSTEIN: Dr.  
5 Gill? I just wanted to confirm that I got  
6 some information correctly from you. It  
7 sounds as though the way you are using the  
8 procedure for your right atrial ablation is  
9 that you're creating two lines, two lesions,  
10 two sets of lesions, one anterior and one  
11 septal. Is that right?

12 DR. GILL: That's right.

13 MEMBER SACKNER-BERNSTEIN: So,  
14 then, that's different than the approach used  
15 in the data from this study?

16 DR. GILL: We don't necessarily do  
17 a flutter line unless it's necessary in our  
18 patients and they present with flutter.

19 MEMBER SACKNER-BERNSTEIN: Okay.  
20 And you also do an anterior line, which is not  
21 part of this approach, correct?

22 DR. GILL: Yes. It's very close to  
23 the line. It depends on whether it's anterior  
24 to the Christa or posterior to the Christa.  
25 And I don't think it makes too much difference

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1 as to whether it's anterior or posterior to  
2 Christa because all we're trying to achieve is  
3 compartmentalization of the atrium.

4 CHAIRPERSON RAMSEY: Okay. We've  
5 got to move on now to the next session. Thank  
6 you both, both speakers, from the open  
7 discussion.

8 OPEN COMMITTEE DISCUSSION

9 CHAIRPERSON RAMSEY: So we are now  
10 going to begin the panel discussion portion of  
11 the meeting. This portion is open to public  
12 observation, and public attendees may view it,  
13 but they are not allowed to participate unless  
14 the panel has a specific request of them.

15 So, as I stated at the beginning of  
16 today's meeting, the panel is charged to  
17 answer the following question and to make a  
18 recommendation to the center director as to  
19 how this scientific dispute should be  
20 resolved.

21 We don't have a slide for the  
22 screen, but the question, which we have seen,  
23 is the following, which is, does the PMA, as  
24 amended, provide valid scientific evidence  
25 that demonstrates a reasonable assurance of

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1 the safety and effectiveness of the Revelation  
2 Tx microcatheter ablation system for its  
3 intended use in the specified patient  
4 population?

5 And what we're going to do is I'll  
6 have the panel members ask questions of either  
7 the sponsor or the FDA. And we'll give them a  
8 chance to respond. And then in the interest  
9 of fairness, I will give the other party a  
10 chance to respond to that response. But there  
11 will be no discussion outside of that type of  
12 a situation.

13 I would ask that you both keep your  
14 responses as brief as possible. I will  
15 maintain a prerogative to cut people off if I  
16 feel they are going on too long, but I would  
17 very much like to avoid that if at all  
18 possible. And, of course, we will have our  
19 panel members ask one at a time.

20 So let us go on. And let me just  
21 throw it open to the panel now, who is free to  
22 ask questions. Yes?

23 MS. WALKER: Just one point of  
24 clarification for the sponsor. In the panel  
25 pack, you have an indications for use

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1 statement. In the executive summary, you also  
2 have an indications statement for use in the  
3 labeling. And they are different. So I was  
4 wondering if you could clarify, please, which  
5 indications statement we are considering here  
6 today.

7 DR. CHER: We would like the panel  
8 to consider the indications statement that we  
9 submitted most recently. Most importantly, we  
10 are aware of limitations with the NavAblator  
11 catheter. And now that there are three  
12 approved catheters for isthmus ablation, we  
13 believe that the panel could give  
14 consideration to improving the Revelation Tx  
15 catheter to make the lateral and septal  
16 lesions and that the instructions for use  
17 include instructions to have the physician at  
18 his discretion perform an isthmus ablation  
19 with an improved catheter.

20 The fundamentals of the indications  
21 statement, however, stay the same. It's the  
22 same patient population.

23 MS. WALKER: Just one follow-up.  
24 Just as far as one indicates drug-refractory  
25 and one does not indicate drug-refractory.

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1 DR. CHER: Yes. It should be  
2 drug-refractory symptomatic paroxysmal atrial  
3 fibrillation. I apologize for the confusion.

4 CHAIRPERSON RAMSEY: Would you like  
5 to respond, FDA?

6 DR. ZUCKERMAN: Yes. We also noted  
7 that the indications for use statement was  
8 different from what was the indications for  
9 use statement that was part of the two "not  
10 approvable" letters. It's my original slide  
11 7.

12 I think there are two issues here.  
13 One is the dispute today is, did the agency  
14 act correctly using the original indications  
15 for use statement in making these two "not  
16 approvable" decisions. I think that is the  
17 main charge of this panel.

18 Certainly from the agency  
19 perspective, we would again maintain that this  
20 was a device system. And we don't have the  
21 data to support this IFU statement.

22 The question just raised by a panel  
23 member really portends to a future development  
24 of this interesting technology. Should it  
25 perhaps be studied with a different catheter

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1 to make the IVC tricuspid line or should it be  
2 used with, as we just saw, an Ensite mapping  
3 system so that we can figure out when we have  
4 completed the procedure in the EP lab, et  
5 cetera? Those are future questions but aren't  
6 at the core of where we are right now, future  
7 questions for a future trial. I'm sorry.

8 CHAIRPERSON RAMSEY: Thank you.

9 Do you have any follow-up on that?

10 I wanted to add to the panel that we can ask  
11 questions of ourselves. And you're welcome to  
12 do that. For those types of questions, I  
13 won't ask necessarily for the sponsor or FDA  
14 unless you specifically request, but you are  
15 certainly welcome. We should talk among  
16 ourselves.

17 MEMBER SLOTWINER: If I may say, I  
18 wanted to point out to Dr. Sackner-Bernstein  
19 Dr. Gill's presentation was on patients who  
20 had pulmonary vein isolation and then a right  
21 atrial ablation. I wasn't sure if that was  
22 clear when you described it.

23 MEMBER SACKNER-BERNSTEIN: It  
24 wasn't. And part of it, though, is trying to  
25 get an understanding of what lesion set you

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1 would tell somebody to use if you were to  
2 decide that the catheter system and/or  
3 catheters were approvable.

4 So I just wanted to make sure I  
5 understood that aspect of it. And so he is  
6 really focusing on AF recurrences in the -- I  
7 presume he is referring to AF recurrences with  
8 an RA source. So he's doing an RA Maze  
9 procedure.

10 MEMBER SLOTWINER: Yes. I think  
11 all the patients he took had previously had a  
12 pulmonary vein isolation ablation and then had  
13 developed recurrent afib, primarily due to  
14 non-pulmonary vein sources. And so yes, this  
15 was an additional set of empiric lesions.

16 MEMBER SACKNER-BERNSTEIN: And as  
17 long as we're talking about lesion sets, I  
18 don't know if you are the best person to  
19 answer this or if maybe there is somebody else  
20 who might have some thoughts. But there is a  
21 lot of discussion comparing this to the Maze  
22 procedure.

23 And, as best I can tell from  
24 looking through drawings, having not done a  
25 Maze procedure or an RF ablation

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1 percutaneously. It doesn't look as though the  
2 lesions are precisely the same.

3           So how important is that? For  
4 example, a Maze procedure does include a line  
5 that looks like it goes a little bit  
6 anteriorly, as this procedure set did in phase  
7 2B, but doesn't include in phase 3? This has  
8 the posterior septal, lateral, and septal.  
9 The two lesions in this look a little  
10 different than what the Maze did in the right  
11 atrium.

12           So I am wondering how much we  
13 should even be paying attention to the history  
14 of the Maze procedure, as opposed to just  
15 looking at this as an independent procedure  
16 and sort of throw that term aside.

17           MEMBER SLOTWINER: By the way, I  
18 think of it as the Maze procedure was the gold  
19 standard that we do use, demonstrating that  
20 isolation of most of the triggers of atrial  
21 fibrillation by isolating the pulmonary veins  
22 and then by debulking the atria, by creating a  
23 series of lines to limit the substrate for  
24 reentrant arrhythmias has been the most  
25 effective procedure for curing atrial

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1 fibrillation.

2           The exact lesion set that was  
3 placed by Dr. Cox nobody has been able to --  
4 we can't create in the EP laboratory. And we  
5 have been struggling to figure out an  
6 endocardial approach with a minimum set of  
7 lesions that has the greatest efficacy.

8           But I don't think comparing right  
9 atrial ablation alone to the surgical Maze is  
10 a fair comparison.

11           CHAIRPERSON RAMSEY:        Sure, Dr.  
12 Hirshfeld. Go ahead.

13           MEMBER HIRSHFELD: This is directed  
14 first to the sponsor. And I expect FDA may  
15 want to reply to this also. This has to do  
16 with the acute effect efficacy assessment.  
17 And there has been a great deal of discussion  
18 about the number of electrograms that were  
19 measured and were reported.

20           And in the FDA panel pack, we were  
21 given some figures. And it turns out that  
22 according to the FDA figures that are on page  
23 14 of section 4B, that there were roughly a  
24 little more than 5 anterior or lateral  
25 remeasurements per patient and about 4

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1 anterior or septal measurements per patient.  
2 And this was what FDA felt was inadequate at  
3 demonstration of comprehensive efficacy.

4 And so I would like to hear from  
5 the sponsor why there are so few measurements  
6 and why they can feel that they can describe  
7 acute efficacy with that number of  
8 measurements.

9 DR. SAKSENA: Well, I think that as  
10 you have looked at the construction of the  
11 catheter, you have the ability to have eight  
12 recordings at each site, at each wall.

13 When you are ablating and ablating  
14 over a period of time, before the ablation,  
15 you may be able to get a certain number of  
16 those recordings. And after the ablation, you  
17 try and get recordings back again to show the  
18 diminution. And you monitor them during that  
19 period.

20 It is not uncommon that one or two  
21 electrodes on an ablation gather during an  
22 ablation procedure may not be getting a  
23 complete recording or a satisfactory  
24 recording.

25 So what we try to do, as has been

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1 discussed here, is that we look at conduction  
2 block, as has been mentioned. But the fact  
3 that electrogram diminution is present in that  
4 large set of data with all of these centers  
5 showing effects in the same direction, as I  
6 said, I review ablation papers every day of  
7 the week for the journal. I have not seen  
8 such large data set.

9 MEMBER HIRSHFELD: Well, I agree it  
10 is a lot of electrograms, but if the  
11 theoretical number of electrograms for a given  
12 line that would be potentially measurable  
13 would be 16. And you're turning in 4 or 5 of  
14 the 16. That seems like a small number.

15 DR. SAKSENA: From what I heard, I  
16 haven't seen it, but I gather it's four per  
17 region septum and four or five on the other  
18 side. So we are actually turning in about  
19 half of what you could have probably seen.

20 MEMBER HIRSHFELD: Well, my  
21 understanding -- and maybe FDA can clarify  
22 this -- is that includes both pre and post  
23 measurements. So those are baseline  
24 pre-ablation measurements and then the  
25 post-ablation measurements also.

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1 DR. CHER: That is correct. I do  
2 want to emphasize, though, that although  
3 electrograms were not collected at every  
4 single electrode for every single patient, I  
5 do believe -- and I believe all of the EPs in  
6 the room would agree with me that the  
7 information that is collected is certainly  
8 sufficient to allow us to know, allow us to  
9 believe that the atria were, in fact, ablated.

10 CHAIRPERSON RAMSEY: What I will do  
11 is I will ask the FDA to have a moment to  
12 respond. And then, Dr. Slotwiner, you can go  
13 ahead and ask your question.

14 DR. EWING: We're putting up a  
15 slide that was in my presentation. And these  
16 are the numbers that were actually derived  
17 from the Cardima raw data submitted after  
18 amendment 6.

19 In the raw data, there were 94  
20 posterior lateral lines produced. And per  
21 that data, there were 1969 lesions, which is  
22 an average of 20 burns per line. So the  
23 missing data is 67 percent of electrograms for  
24 that line.

25 The more important number I think

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1 -- there are two different ways to look at  
2 this, that we really do need to know that each  
3 application of energy was effective, but we  
4 also need to know that whether each patient  
5 had an effective procedure or not and the  
6 company has never presented a number of  
7 patients that had an effective procedure. And  
8 they stated that they do not have that data.  
9 They have always stated that they cannot  
10 produce the data to show that any individual  
11 patient had an effective line of lesions.

12 There are multiple different types  
13 of mapping produced. And you have heard  
14 people speaking this morning, talking about  
15 the importance of mapping. The mapping data  
16 was not ever submitted to the FDA. So we do  
17 not know if any patient ever had any effective  
18 line of lesions.

19 CHAIRPERSON RAMSEY: Dr. Slotwiner?

20 MEMBER SLOTWINER: Yes. I wanted  
21 to ask the sponsor if they could elaborate  
22 more on that point. In their presentation,  
23 there are three slides that I have on the  
24 amplitude measurements from the ablations.  
25 And can we agree that amplitude reduction with

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1 each ablation is required to show acute  
2 efficacy?

3 DR. CHER: I actually believe the  
4 answer is no. And I actually don't think  
5 anyone in the room believes that. I will let  
6 the EPs speak, but I think in general we do  
7 not need to see amplitude reduction at every  
8 single electrode. It's not feasible, and it's  
9 not possible. And in many cases, the  
10 electrode may be in a location where the  
11 electrophysiologist does not want to do an  
12 ablation.

13 Let me ask the electrophysiologist  
14 to comment here.

15 DR. KOCHERIL: I think it is a  
16 mistake to equate a line of lesions with a  
17 number of electrogram amplitudes. I mean,  
18 what do we do? I have been at a variety of  
19 trials.

20 What we do most of the time is, you  
21 know, a visual look at the electrograms. And  
22 when the electrogram amplitude drops, you are  
23 done with that spot and you move on to the  
24 next lesion. And many EPs work that way.

25 I don't know all the reasons why we

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1 don't have all of those numbers, but, you  
2 know, we can't equate a certain number of  
3 recordings with a complete line. That doesn't  
4 compute.

5 I mean, it seems reasonable to say  
6 that if you showed an Ensite map, then you did  
7 show a line of block. Even if you went with  
8 the pacing idea, you know, there are  
9 situations where you try to measure pacing  
10 across the line of block and you can't capture  
11 because you ablate tissue. And there are all  
12 kinds of reasons why all the techniques that  
13 are employed aren't going to work well.

14 But I think what we have done is we  
15 have shown that we have a certain amount of  
16 data, we have clinical success. I think  
17 basically we have shown a bunch of results  
18 that are going in the same direction.

19 So I think our patients did benefit  
20 from the ablation procedure, but, you know, as  
21 you have seen, there are some holes in the  
22 data.

23 MEMBER SLOTWINER: That data that  
24 is presented in those slides, the data that  
25 you do have, is that from one electrode in one

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1 spot before an ablation comparing the same  
2 patient, the same physician, the amplitude  
3 after that ablation?

4 DR. CHER: That's correct. The  
5 figure that we submitted in the January 2004  
6 PMA, the figure with the diagonal line, those  
7 are paired measurements.

8 So, just to summarize, electrogram  
9 measurements were available from 87 percent of  
10 patients. And there were paired measurements  
11 from at least one electrode in 78 percent of  
12 patients. It's those paired measurements that  
13 I presented in that graph that you saw that do  
14 show reductions in electrode amplitudes.

15 I would like to actually ask Dr.  
16 Saksena to comment if that's okay.

17 DR. SAKSENA: I sensed a little bit  
18 of confusion here about this electrogram  
19 issue. Let me clarify it by making a very  
20 simple illustration. You might remember that  
21 I showed you a video of an anterior  
22 compartment and a posterior compartment done  
23 on a patient that we did an Ensite map on last  
24 week.

25 If I ran you through those lesions,

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1 I would tell you that of those 60 lesions that  
2 were done, more than half of them did not show  
3 a reduction in electrogram amplitude. But it  
4 was a complete line of block.

5 What happens is when you have the  
6 electrode at the tissue and there is edema  
7 around the tissue -- and this goes back to our  
8 RF studies 15-17 years ago -- you can pick up  
9 electrical activity from the edematous zone.  
10 If all the tissue has not died completely, you  
11 still get some signal.

12 So the electrogram amplitude is  
13 helpful when it is there, but it is not  
14 mandatory to get the line of block.

15 CHAIRPERSON RAMSEY: Thank you. I  
16 think it's time to let FDA weigh in. Thank  
17 you.

18 DR. EWING: Thank you.

19 I think that it is important to go  
20 back to the clinical trial protocol. And we  
21 will show another slide that was from the  
22 presentation this morning where the protocol  
23 states that it was mandatory for the  
24 electrograms to be measured per energy  
25 delivery.

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1           And these measurements were to be  
2 sent to a core lab. It was set up to be  
3 prospectively measured in the study. And this  
4 is the way the study was set up to tell us  
5 that each individual patient was treated  
6 successfully or not.

7           It would be wonderful if we had  
8 more mapping information, but this is the way  
9 the protocol was set up. And this is the only  
10 way that the information was to be given to us  
11 whether the patient was a success as an  
12 example of how the investigators may have used  
13 the catheter differently or we don't know how  
14 the catheter was used.

15           So we cannot construct future users  
16 of the catheter on how to replicate,  
17 potentially replicate, the study results.

18           CHAIRPERSON RAMSEY: Any more  
19 comments?

20           (No response.)

21           CHAIRPERSON RAMSEY: We do ask that  
22 you turn that off after you are done with the  
23 presentation.

24           Yes, please?

25           MEMBER SCHMID: I am actually

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1 struggling here more than everyone else is as  
2 I really have no experience with these  
3 procedures whatsoever, but let me see if I can  
4 understand the difficulty with the numbers  
5 here.

6 As I understand it, 78 percent of  
7 the patients had paired measurement. Is that  
8 correct?

9 DR. CHER: They had at least one  
10 paired measurement. That's correct.

11 MEMBER SCHMID: So 78 percent had  
12 at least one paired measurement. However, if  
13 all of the electrodes had been working, then  
14 you would have had 16 paired measurements. Is  
15 that correct?

16 DR. CHER: That is not correct. As  
17 we just discussed, it is highly likely that in  
18 some positions, the physician may decide not  
19 to fire the electrode. In that case, we would  
20 not collect --

21 MEMBER SCHMID: I understand. But  
22 the maximum number would be 16 if everything  
23 was working. What I am trying to understand  
24 is how the FDA is saying that 90 or 80 percent  
25 of the measurements are missing and you are

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1 saying that 80 percent are present.

2 DR. CHER: Well, I think it is a  
3 bit of a misconception. We also have to  
4 understand that in some patients, the atria  
5 are smaller than in other patients. And in  
6 that case, the entire atrium from top to  
7 bottom may be covered by a single application  
8 of the catheter with fewer than eight  
9 electrodes. So here is another example of a  
10 case where not all eight electrodes need to be  
11 fired to treat the patient.

12 MEMBER SCHMID: So if 78 percent of  
13 the patients have at least one paired  
14 measurement, what you're saying, then, is that  
15 if there is one paired measurement, that may  
16 be sufficient to make the determination?

17 DR. CHER: No, I am not saying  
18 that. What I wanted to do was some data  
19 analysis. And the data analysis I wanted to  
20 do was to look at the per-electrode reduction  
21 from before to after.

22 I am certainly not saying that one  
23 electrode measurement for a patient is  
24 indicative that the patient had a successful  
25 ablation. I assume and based on some of the

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1 procedures that I saw the physicians who  
2 participated in our study used the catheter as  
3 we instructed them to as it was very clearly  
4 written in the instructions for use and in the  
5 clinical trial protocol to ablate and place  
6 the lesions that they placed. I have no  
7 reason to assume that the physicians would put  
8 the catheter in and not do what they were  
9 supposed to do.

10 MEMBER SCHMID: Thank you.

11 CHAIRPERSON RAMSEY: FDA?

12 DR. ZUCKERMAN: Yes. We would like  
13 Dr. Ewing to talk to ablations.

14 DR. EWING: I will show this slide  
15 again. On each line for the study or  
16 posterior lateral line, there are 94 lines.  
17 And there are 95 for the posterior septal.

18 The average number of burns or  
19 application of energy was 20, almost 21 for  
20 the posterior lateral and almost 18 for the  
21 posterior septal. We do not have evidence for  
22 how or why the investigator decided to use the  
23 number of burns that they did. So if there  
24 were an average of 20, if one patient received  
25 20 burns, that would be 40 measurements.

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1 CHAIRPERSON RAMSEY: Yes, please?

2 MS. WHITTINGTON: You did a real  
3 good job of showing us what the physicians  
4 were instructed to do as far as doing the  
5 procedure. Can you give me those same  
6 explicit instructions on what data points they  
7 were to collect? Was that equally as clearly  
8 defined?

9 DR. CHER: It was not as clearly  
10 defined in the protocol because we had to let  
11 physicians do ablation as they saw fit.  
12 Please note, though, that the case report  
13 forms did include spaces for physicians to  
14 write in electrode amplitudes that they did  
15 perform.

16 So, again, we relied on the  
17 expertise of physicians who are very familiar  
18 with the application of radiofrequency  
19 catheter in the right atrium to do what they  
20 thought was best but along the lines of making  
21 a lateral and a septal lesion using all of the  
22 electrodes that were appropriate.

23 MS. WHITTINGTON: I interpreted  
24 your presentation initially that they were to  
25 collect data points on each piece. And I

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1 think the FDA has done the same thing. And  
2 that's what was clear to me.

3 So to say that I am very explicit  
4 on what to do but let them have their own  
5 ideas in how they do it, I can't imagine. I  
6 don't understand not having explicit data  
7 point collection.

8 And, in tandem to that, I'm asking  
9 compound questions here. But the FDA did site  
10 visits with no reports of issues. So I would  
11 think if they had a data collection form that  
12 had blanks in it, that would be a red flag and  
13 they would be looking for those things.

14 DR. SAKSENA: Well, perhaps I can  
15 speak to just the data that we collected at  
16 our center. We did collect electrograms at  
17 each of the electrodes that we felt was in the  
18 appropriate pace. So it was not one electrode  
19 at one point.

20 And, in fact, we did 3D mapping, as  
21 you can see, because when we take on new  
22 technology, we want to validate it even  
23 further. And I showed you a 3D map with a  
24 line of block.

25 I think that what I think everybody

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1 is struggling with is why; for example, the  
2 analysis that was just made by the FDA on the  
3 number of burns divided by the potential  
4 possibilities.

5 We do burns for a number of  
6 reasons. We do safety burns. For example, if  
7 we do a burn at one site and we see the  
8 electrogram go down, we do another burn right  
9 at that site, we want to look at it further or  
10 we think that is an efficacious site. So that  
11 is a completely fallacious analysis looking at  
12 the number of burns and trying to extrapolate  
13 the number of electrograms that you should  
14 have had.

15 So, unfortunately, the science of  
16 catheter ablation has not advanced to the  
17 degree of precision that all of us would like  
18 to see as a mathematical analysis like this.  
19 And I think we have got some very unrealistic  
20 expectations of clinical data in some of these  
21 situations.

22 Many of these trials that we  
23 consider landmark trial have not even provided  
24 anything more than a few electrogram  
25 recordings being extinguished, say, in the

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1 pulmonary vein.

2 CHAIRPERSON RAMSEY: Thank you. I  
3 believe FDA would like to comment, too.

4 DR. EWING: I can comment on the  
5 data auditing. The BIMO inspections would not  
6 have audited the information that should have  
7 been collected and sent to the core lab. They  
8 would be looking at the case report forms,  
9 slightly different analysis.

10 I think it is also important to  
11 remember when we are thinking about clinical  
12 trials and trials that are in the literature.

13 They are relating more for clinical practice,  
14 clinical research, rather than trying to  
15 investigate with very specific device works or  
16 not and how can we instruct new users how to  
17 use that device.

18 CHAIRPERSON RAMSEY: Do you have  
19 any other comments?

20 DR. SAKSENA: No.

21 CHAIRPERSON RAMSEY: Okay. Did you  
22 have a comment, Dr. Sackner-Bernstein,  
23 question?

24 MEMBER SACKNER-BERNSTEIN: I had a  
25 question. One of the slides that Dr. Cher put

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1 up during the rebuttal, I just wondered if you  
2 could put it back up again. You showed for a  
3 selected subset of sites the numbers that  
4 relate to how many recordings were done of  
5 electrograms. Can you put that back up again?

6 It went by pretty fast. I had a question  
7 about it.

8 DR. CHER: Sure. I'm sorry. I  
9 don't have the capability myself. I'm relying  
10 on someone else.

11 MEMBER SACKNER-BERNSTEIN: So while  
12 that comes up, there was a question,  
13 Christopher, you asked before about the one  
14 measure versus 16. It looks like the way that  
15 FDA slide looks, it was really then at least  
16 80-some odd percent had one recording;  
17 whereas, the average was about 38 that they  
18 should have had is the way I would look at  
19 that because the average number of lesions was  
20 38. And they're saying they had at least one.

21 So on this slide, I just thought it  
22 was interesting to look at this just so I  
23 understood what was going on. What do these  
24 numbers mean in the grid? I mean, I see the  
25 electrode numbers. I see the number of

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1 patients.

2 Does this mean, for example, that  
3 investigator number ten out of eight patients,  
4 four had electrode one readings before and  
5 three afterwards? I don't think that's what  
6 that means because if I look at the fourth  
7 line where there are 15 patients, there were  
8 23 recordings at electrode one in a lateral  
9 lesion before.

10 So what does this mean?

11 DR. CHER: Your interpretation is  
12 actually correct. On the left-hand column --  
13 could you put it back, please? Thank you.

14 For example, for investigator  
15 number ten, for lateral lesion, electrode  
16 number one, there were four before  
17 measurements and for lateral lesion, electrode  
18 number one, there were three after  
19 measurements, same thing for all the rest of  
20 the entries in the row.

21 It is possible that a physician may  
22 make more than one before and more than one  
23 after lesion. This can occur if the physician  
24 moves the electrode and ablates again. We  
25 would have a before/after measurement for the

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1 first ablation and a before/after measurement  
2 for the second ablation.

3 CHAIRPERSON RAMSEY: Dr. Hirshfeld  
4 had a question.

5 MEMBER HIRSHFELD: Yes.

6 CHAIRPERSON RAMSEY: Oh, FDA. I'm  
7 sorry. I didn't give you a chance. Did you  
8 want to say anything?

9 (No response.)

10 CHAIRPERSON RAMSEY: No. Okay.

11 MEMBER SACKNER-BERNSTEIN: Before  
12 you go on, can I ask that slide to stay up for  
13 a second? I just want to look at it while you  
14 are going to the next question or something.

15 MEMBER HIRSHFELD: Actually, my  
16 question could be amplified by the data that  
17 are on that slide.

18 MEMBER SACKNER-BERNSTEIN: Okay.

19 CHAIRPERSON RAMSEY: Yes. Please  
20 let's leave it up.

21 MEMBER HIRSHFELD: I just want to  
22 restate this to make certain that I understand  
23 this because, as I understand, the theory of  
24 this procedure is that you create a continuous  
25 lesion, linear lesion, over the entire extent

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1 that you are to burn. And so the lesion would  
2 basically be approximately the length of the  
3 entire electrode carrying portion of the  
4 catheter.

5 So if you make an electrogram  
6 measurement at one or maybe two points along  
7 that line, how does that document that you  
8 have actually created a complete lesion over  
9 the entire length that you intended to ablate?

10 DR. CHER: You have a good point  
11 there. If we have only one measurement,  
12 clearly this indicates to us that the amount  
13 of data collection we have is insufficient to  
14 make that judgment.

15 However, again, I repeat that  
16 physicians use the catheter as was instructed.

17 They had no reason not to. I believe and I  
18 believe all the electrophysiologists in the  
19 room will be able to tell you that they used  
20 the catheter as directed to make all of the  
21 prescribed lesions.

22 The fact that we don't have all  
23 data on every single electrode I don't think  
24 impairs our ability to interpret the data that  
25 we do have and to come to the conclusion that

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1 ablations were made.

2 I remind the panel that technology  
3 to assess conduction block, the Ensite probe  
4 was not available during the early part of the  
5 study. It was available towards the later  
6 part, and some of the physicians used it,  
7 including the physicians in the room. And  
8 they were able to demonstrate block.

9 I would like to ask Dr. Saksena to  
10 comment as well.

11 DR. SAKSENA: Just a small  
12 clarification. You know, we live in linear  
13 lines. And we always talk about having  
14 complete lines and transmural lines and  
15 getting a complete line of block, like Jim Cox  
16 did with his incisions.

17 Unfortunately, reality is not  
18 there. In fact, what we actually do is we get  
19 skip lesions, what we call skip lesions. So  
20 when these ablation patients go to the  
21 operating room for a redo or a bypass, you see  
22 these skipped areas that we have missed.

23 So how does it work if you have got  
24 these gaps? The reason is because of the  
25 frailty of maintenance of tachycardia. What

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1 happens here is that tachycardias become  
2 unstable and can't maintain themselves, even  
3 though there is a little gap left in the line  
4 or there is edema and partial thickness  
5 ablation and not full thickness ablation.

6 So what we actually see on the  
7 Ensite map is that the electrical propagation  
8 gets altered. That doesn't mean that there is  
9 an anatomic wall. And I think that is often  
10 an area of confusion.

11 And I think people who listen to  
12 ablation lectures go away with expectations  
13 and thoughts that are far a little bit removed  
14 from the pathologic reality of what happens in  
15 humans.

16 And that also explains why you are  
17 not getting all of these electrograms because,  
18 as you saw, that interior topographical map of  
19 the Christa, one electrode is bouncing around.

20 Of that one-minute lesion, 30 seconds might  
21 be in contact and create a partial thickness  
22 burn. The other 30 seconds is floating in the  
23 blood pool but not getting an electrogram.  
24 So, unfortunately, it is still a developing  
25 science.

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1 CHAIRPERSON RAMSEY: Thank you.

2 FDA, would you like to respond?

3 DR. EWING: Thank you.

4 One thing that I think is important  
5 for us to remember is that to assess the  
6 effectiveness of the device, we need to know  
7 which patient had an effective procedure and  
8 then correlate the ultimate outcome of the  
9 patient with whether they had an effective  
10 procedure.

11 And if the total amount of this  
12 information had been collected, we might be  
13 able to tease out these factors of which  
14 patients had maybe an incomplete line and what  
15 happened to them. Because we do not have this  
16 data, the data was not recorded, we can't even  
17 do -- I mean, I guess I am suggesting  
18 something like a post hoc analysis, but we  
19 can't figure out which patient was treated  
20 better or more effectively than others. And  
21 this slide shows the clinical effectiveness  
22 per site.

23 And, as Dr. Zuckerman mentioned  
24 earlier, you can see there's a wide variety of  
25 success per site. And it would be helpful for

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1 us to know what is it that the more successful  
2 sites did with the catheter to be more  
3 effectively ablating, maybe, than the other  
4 sites.

5 But, as it is right now, we cannot  
6 correlate the EP procedure, the ablation  
7 procedure with what happened with the patient.

8 CHAIRPERSON RAMSEY: Okay. Yes.  
9 Dr. Browner has been waiting patiently. So  
10 your turn.

11 MEMBER BROWNER: This is a question  
12 for the sponsor. I am assuming that during  
13 the earlier phases of the study, phase 2  
14 studies, that this problem of incomplete data  
15 collection vis-a-vis the acute effects of the  
16 procedure became apparent.

17 And so I am puzzled as to whether  
18 you considered having some sort of minimum  
19 objective data set that could address this  
20 question because right now what the panel is  
21 having to struggle with is what I am hearing  
22 you say, that, in effect, you judged acute  
23 efficacy based on the judgment of the  
24 investigator, rather than on any sort of  
25 objective criteria that we could review from

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1 the point of view of data.

2 Is that a fair summary of what  
3 happened? And why didn't you use a minimum  
4 data set of some sort?

5 DR. CHER: Let me first say that I  
6 wasn't present at the beginning of the trial.

7 So it is difficult for me to comment on what  
8 happened in the phase 2 and the early parts of  
9 the phase 3 study.

10 I would like to focus the panel's  
11 attention on comments from the 1998 panel  
12 meeting, in which this issue was discussed by  
13 a number of electrophysiologists. They in  
14 1998 came to the conclusion that there was no  
15 acute endpoint, similar to that which we use  
16 in other studies; for example, isthmus  
17 ablation or AV nodal reentrant tachycardia  
18 ablation that predicts long-term success.  
19 There was a substantial discussion. And they  
20 decided, they recommended that we judge the  
21 success of the procedure by ablating according  
22 to the instructions for use and then looking  
23 at how the patients do in chronic follow-up.

24 Still, in left atrial ablation --  
25 and perhaps the electrophysiologists on the

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1 panel can talk about this. There are still  
2 very few acute procedure endpoints that are  
3 known to be predictive of long-term success.

4 So, instead, the approach we took  
5 was let's ablate the patients according to a  
6 preset pattern according to the protocol. And  
7 then let's look at chronic effectiveness and  
8 see how we do.

9 CHAIRPERSON RAMSEY: Go ahead.

10 DR. EWING: We have a slide that  
11 shows data that was acquired during phase 2,  
12 early on in phase 2, and shows that this is  
13 electrogram measurements pre and post.

14 So I believe, although I also was  
15 not involved with this study back at this  
16 time, that the agency expected to see this  
17 kind of data for all the patients at the end  
18 of the study. It was a per-protocol required  
19 measurement to be evaluated by a core lab.

20 DR. CHER: I'm sorry. It is  
21 difficult for us to comment on this  
22 feasibility study. This is different than a  
23 multi-center trial.

24 CHAIRPERSON RAMSEY: Okay. Go  
25 ahead.

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1                   MEMBER     SLOTWINER:           As     the  
2     electrophysiologist on the panel, it is hard.

3     I would agree that we don't always see the  
4     amplitude reduction that we would like to see.

5     And that doesn't always mean the ablation  
6     lesion is ineffective, but I can't imagine  
7     continuing to ablate without some endpoint,  
8     perhaps checking for a line of block or  
9     electrical isolation as we do with pulmonary  
10    veins.

11                   And so it is difficult for me to  
12    understand if I were to have this catheter  
13    what I would be looking for unless I used  
14    Ensite or some other mapping system as an  
15    endpoint.

16                   DR.    SAKSENA:           I think it is  
17    important, Dr. Slotwiner, to think of the time  
18    and frame in which this study was done. And,  
19    you know, this was in the early days of  
20    catheter ablation. We know a whole lot more  
21    ten years later about what we should do.

22                   So at those times, we usually had a  
23    temperature target and anatomic location. And  
24    sometimes that was all you had. So I think  
25    it's important to realize that I am not trying

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1 to make a justification for a lack of more  
2 data. We would like to have it. I have just  
3 some of these data very recently.

4 I think that it is a far leap to  
5 say that because you don't have all the  
6 procedural data, that, therefore, we cannot  
7 guide the procedure today in 2007. And, more  
8 importantly, we all know that what you see  
9 during the ablation procedure does not tell  
10 you how the patient does three months and  
11 beyond.

12 So, in fact, currently we even  
13 don't pay any attention to what happens in the  
14 first month after ablation. We all tell our  
15 patients, "Don't get upset if you've got a  
16 recurrence in the first month. Come back  
17 after six weeks. You may even need a  
18 cardioversion."

19 So, really, I think in terms of  
20 clinical practice, really, this hinges in my  
21 mind on the belief of clinical success on a  
22 chronic basis.

23 MEMBER SLOTWINER: I fully agree  
24 with your comments that we do see atrial  
25 fibrillation following ablations frequently.

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1 And we do reassure our patients, but we do  
2 have an endpoint for those procedures. And it  
3 is different here.

4 We are looking at a new technology;  
5 whereas, with the pulmonary vein isolation,  
6 the concept is different. We have many  
7 different tools to do that. And I think it is  
8 comparing apples to oranges.

9 DR. SAKSENA: Well, I think, again,  
10 as I said, it was ten years ago when the  
11 Ensite system was not as easily available. A  
12 lot people didn't go to the trouble of to do a  
13 mapping, a base on each side, look at strict  
14 potentials, do all of this. It was all fairly  
15 difficult, and there were a lot of catheters  
16 being put in.

17 So I think that some of it has to  
18 do with the infancy of the field. And I think  
19 it's easy for us to look back at 2007 and for  
20 me to show you last week's Ensite map. I  
21 wasn't doing them at that time when this was  
22 being done, starting up.

23 DR. KOCHERIL: If I could just add?  
24 So in the trial, basically the investigators  
25 were given instructions to put down to

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1 complete lines. And I wasn't at every site,  
2 obviously, but I have seen that the  
3 investigators were very compulsive in making  
4 sure that the lines were done.

5 Now, sometimes how it happens is  
6 you get to a lesion or you put your catheter  
7 down and you're looking at the next electrode  
8 and you see a very small signal. And an  
9 investigator could choose not to ablate there  
10 because that's already damaged tissue, perhaps  
11 from the lesion right before it. So there are  
12 reasons to move on and not specifically make a  
13 measurement there.

14 I can also tell you that ten years  
15 ago this was a very long procedure, even  
16 though, you know, today it sounds very  
17 straightforward and getting a recording at  
18 every one of those electrodes would make a  
19 very long procedure.

20 So with the investigators in  
21 general, I think that it was to get where you  
22 had a good signal, measure it, see it go down,  
23 measure it afterwards, and that was what was  
24 entered.

25 So, I mean, again, that's not an

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1 excuse for the wholes, but, I mean, there is a  
2 practical reality in how these procedures were  
3 done. And I think the investigators did make  
4 every effort to make sure there were complete  
5 lines by going over the lines in some cases,  
6 again, if needed, and confirming that you had  
7 scar potentials.

8 CHAIRPERSON RAMSEY: Would you like  
9 to comment, FDA? You certainly don't have to.

10 DR. ZUCKERMAN: You know, I think  
11 Dr. Slotwiner's comments are quite pertinent  
12 and what is the problem that the FDA has  
13 struggled with for the last four years that we  
14 have had this application in-house.

15 CHAIRPERSON RAMSEY: Yes?

16 MEMBER SCHMID: Okay. We're at the  
17 risk probably of beating a dead horse here.  
18 So I'm still struggling with this. So one of  
19 the things that we're charged with doing is  
20 making a decision as to whether this -- you  
21 know, there are three choices we have. And  
22 one of them is to impose conditions.

23 And I have been told that one of  
24 the things that we could ask to do is to have  
25 the data reanalyzed. So what I am trying to

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1 get a sense of is whether these data exist for  
2 this reanalysis.

3 Now, it seems to me that from my  
4 point of view here of looking at things as a  
5 mathematic, that if you think of the patients  
6 as being rows and the measurements on each  
7 patient as being columns, then on each  
8 patient, there are going to be some  
9 measurements.

10 And I accept that some of them just  
11 can't be made or weren't made, but presumably  
12 on each patient, there are some measurements  
13 made. And from those measurements, whatever  
14 the endpoint was, the clinician makes a  
15 decision as to whether the line is there or  
16 not.

17 Now, presumably you have these data  
18 or at least this decision was made on each  
19 patient. I am wondering whether the data  
20 exist and whether the FDA has it so that they  
21 could look at those data and say, "We" either  
22 "agree" or "don't agree with your decision.  
23 We" either "think there is enough data" or  
24 "there's not."

25 Now, they may think that every

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1 single one of those cells has to be filled in.

2 You may think that's not the case. But are  
3 there data available so that this thing could  
4 be looked at or are there not?

5 DR. CHER: Yes, there are data  
6 available. Those are data that I have  
7 analyzed. I believe FDA has analyzed the same  
8 data set. So they are available on the basis  
9 that you talked about.

10 DR. EWING: The slide that I have  
11 shown several times with the red circle  
12 showing 100 percent of patients with missing  
13 data, that is our analysis of that data. So  
14 we do not feel that there is sufficient data  
15 to determine if any patient had a successful  
16 line of lesions.

17 And the company actually always has  
18 told us that, that they cannot identify which  
19 patient had a successful procedure or not.

20 DR. CHER: May I comment?

21 CHAIRPERSON RAMSEY: Very briefly.

22 DR. CHER: We do believe that all  
23 of the patients did receive ablations. And we  
24 can identify based upon chronic effectiveness  
25 which patients were successes. I highly

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1 disagree with the notion that just because at  
2 patient is missing a few electrogram  
3 amplitudes, that we can't call the success  
4 that we eventually observe in that patient a  
5 successful treatment.

6 CHAIRPERSON RAMSEY: Okay. I want  
7 to move on. I think, as was said, we have  
8 beat this one about acute procedural  
9 effectiveness quite well. I would like to  
10 move on to another major concern of FDA, which  
11 is chronic clinical effectiveness of the  
12 system. So I would ask the panel members if  
13 they have questions on that point, to please  
14 go ahead.

15 Dr. Browner?

16 MEMBER BROWNER: So if the FDA  
17 could put up its slide number 47? I would  
18 like to hear the sponsor comment on each of  
19 the 28 disputed chronic clinical success  
20 patients because to me, a lot of what we are  
21 being asked to judge hinges on whether there  
22 were successes in 49 patients or in 21  
23 patients.

24 This is a slide from the original  
25 presentation, slide number 47. And it's

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1 labeled "Fifty-seven Disputed Chronic Clinical  
2 Success Patients."

3 CHAIRPERSON RAMSEY: So the  
4 question is for the sponsor.

5 DR. CHER: I'm sorry, but it is  
6 unclear to me whether this is a combination of  
7 phase 2 and phase 3 data. The analysis that I  
8 did was phase 3 only.

9 PARTICIPANT: Phase 3.

10 DR. CHER: The analysis that I did  
11 was to review the medications that each  
12 patient received, the medications to which the  
13 patient was refractory, medications at  
14 baseline, medications required at three months  
15 and at six months.

16 I also reviewed pacemakers that the  
17 patients received. I cannot do this by heart.

18 And I apologize. But in that analysis that I  
19 have done, I found that 12 patients who  
20 received new anti-arrhythmic drugs, for which  
21 I think it is reasonable to ask the question  
22 whether we observed any acute effects.

23 And then with respect to pacemaker  
24 treatment, I evaluated that in a much more  
25 clinical way looking at the literature to help

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1 us understand whether pacemakers would affect  
2 this treatment at all. And it did not.

3 Can I have that slide put up there?

4 No, this is not my slide. No. Let's take  
5 that off.

6 So, again, at this time I cannot  
7 comment. I don't know the clinical history of  
8 every single patient by heart. And I'm not  
9 sure that that's a reasonable request at this  
10 point.

11 Can I just ask Dr. Saksena to  
12 comment?

13 DR. SAKSENA: Yes. Perhaps we can  
14 put up the FDA slide. And maybe I can help as  
15 far as this slide a little bit. Let's look at  
16 what's up there and let's look at later what  
17 we know is existing data.

18 The first issue is anti-arrhythmic  
19 drugs. There's amiodarone, and there's all  
20 else. Okay? For practical purposes, that's  
21 how we look at it.

22 So of these patients, six got  
23 amiodarone, either a dose increase or new  
24 administration. Those are the only ones that  
25 we can make a rational case for that might

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1 have an impact on drug efficacy. There is no  
2 data that says that switching to flecainide,  
3 sotalol, diltiazem, atenolol, or propafenone  
4 will provide efficacy in a patient who has  
5 failed three drugs.

6 As all of our work is done in  
7 patients who are on anti-arrhythmic drugs,  
8 there couldn't be a clinical trial done today  
9 or any day if you withdrew all anti-arrhythmic  
10 drugs in every pacemaker. So what we have to  
11 do is look and see of those drugs what would  
12 make a meaningful difference. And you could  
13 make the case for amiodarone.

14 Non-protocol catheter, this is the  
15 isthmus burn issue, the prophylactic flutter  
16 line in a patient who had not had flutter.  
17 There has never been a study that has shown  
18 flutter ablation has cured atrial fibrillation  
19 or reduced AF episodes.

20 So the whole business of the  
21 non-protocol catheter, yes, it's a glitch. It  
22 doesn't fit the protocol wording that was  
23 there. They didn't use the right catheter.

24 Does it mean that use of the  
25 non-protocol catheter resulted in those

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1 patients becoming effective? We use those  
2 non-protocol catheters every day of the week.

3 Patients don't get better from atrial fib.

4 The pacing data, I suspect that I  
5 have probably the nation's largest experience  
6 in pacing for atrial fibrillation in my  
7 center. And I can tell you in a multi-center  
8 study that we published in JAC for years ago  
9 that we showed conclusively with a randomized  
10 control arm of no pacing that single-site  
11 pacing and dual-site pacing and the absence of  
12 drug therapy do nothing and single-site pacing  
13 does nothing, even the presence of drug  
14 therapy. So none of these patients got a  
15 dual-site pacemaker.

16 The entire batch of stuff, where  
17 pacemakers become an exclusion for success,  
18 yes, technically they are. Practically do  
19 they meet, do they interfere with the  
20 interpretation of clinical success? The  
21 answer is no.

22 So when you parse this whole thing  
23 out, the only thing that I will say  
24 objectively here is the use of new amiodarone  
25 therapy in four patients. And you can

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1 determine if 4 patients getting amiodarone  
2 looking at a firm substudy by the response  
3 rate of 60 percent, what that would mean in a  
4 patient sample of success of 59.

5 CHAIRPERSON RAMSEY: Would you like  
6 to comment?

7 DR. CHER: And the last two lines?

8 DR. SAKSENA: Well, you would have  
9 to comment on that, Danny. I don't know the  
10 answer.

11 DR. CHER: With respect to the  
12 second to last line, I cannot comment. I only  
13 call patients who had threshold when the  
14 measurements were available who had threshold,  
15 decreases to be successes. So it's hard for  
16 me to comment on that.

17 There were two patients that I  
18 called successes based upon their responses to  
19 the atrial fibrillation symptom score. These  
20 were patients who are not compliant with the  
21 TTMs, but they reported to the physician at  
22 six months. So they had tremendous  
23 improvement in symptoms. I think those could  
24 also be reasonably disputed.

25 CHAIRPERSON RAMSEY: Let me give

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1 FDA a chance to respond.

2 DR. EWING: It's important to  
3 remember that our analysis was per protocol  
4 and the patients were required to be on the  
5 same medicines or reduced dosage and to not  
6 have a pacemaker to be considered a success.  
7 And that's per protocol.

8 The other thing that is important  
9 to remember is we are talking about resolution  
10 or reduction in symptoms. We're not talking  
11 about medicines making all the atrial  
12 fibrillation go away. It is entirely  
13 plausible to me that a patient that is given a  
14 new medicine could have a deep or could have  
15 more rate control and could have less  
16 symptoms.

17 So what we are talking about here  
18 is not anti-arrhythmic drugs taking care of  
19 all of the AF. It's helping reduce the number  
20 of symptoms because we're comparing symptoms  
21 at baseline, number of symptoms, number of  
22 self-reported symptoms, compared to number of  
23 self-reported symptoms at six months.

24 The other important thing with this  
25 discussion about the cavo-tricuspid isthmus is

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1 that it was always agreed throughout the trial  
2 that a use of a non-protocol catheter would  
3 render that patient a non-success of the  
4 trial.

5 And we do have one literature  
6 result that we can show you that shows that  
7 there can be some impact in cavo-tricuspid  
8 isthmus in the perception of symptoms. And it  
9 can impact whether the patient would have a  
10 decreased or increased number of symptoms at  
11 six months.

12 The problem is that the trial is  
13 never conducted in a way that would allow us  
14 to pick out whether one lesion set was  
15 effective versus another lesion set.

16 CHAIRPERSON RAMSEY: Go ahead, Dr.  
17 Sackner-Bernstein.

18 MEMBER SACKNER-BERNSTEIN: We have  
19 heard some discussion about operational issues  
20 surrounding the procedure itself in terms of  
21 what data were collected and what catheters  
22 were used.

23 I'm concerned about operational  
24 issues that may relate to characterizing the  
25 population as well as operational issues that

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1 go toward understanding the data long term.

2           There are a couple of things. And  
3 I'm sorry that one of them will involve the  
4 procedure just to give me a context here. In  
5 the FDA panel pack, the second volume, one of  
6 the PA excerpts, it describes how the acute  
7 procedure was described.

8           In case you want to look at section  
9 18, page 111, where it talks about the  
10 operative notes and case report forms being  
11 audited in July of 2003, I'm concerned about  
12 that because I'm not sure who prepared those  
13 operative reports.

14           And if that's information that's  
15 substantially different than what was recorded  
16 during the procedure, it raises issue about  
17 which data should be used. And it also raises  
18 questions in my mind about which data were  
19 used in the analysis.

20           And it goes beyond that. There are  
21 issues of the central core lab looking at the  
22 rhythm strips. It appears -- and this is a  
23 question I really just want to make sure I  
24 understand the answer to. But it appears as  
25 though the core lab managing the strips was

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1 changed in the middle of the trial.

2 Now, it's not clear to me whether  
3 it was changed between phase 2B and phase 3 or  
4 within phase 3, but I think that any time you  
5 are changing core labs in a spirit of data  
6 management integrity, part 11 compliance kinds  
7 of issues, you would want to see validation of  
8 the data-handling procedures.

9 The second core lab had a problem  
10 with their database crashing. And,  
11 fortunately, they had hard copies, but two  
12 patients were lost from the database.

13 It gives me some concern as to how  
14 these were handled. There also were issues in  
15 the study flow chart, the patient outcomes,  
16 and what happened to them with some patients  
17 who looked like they were withdrawn from the  
18 analysis of efficacy well into the trial  
19 because they come out on the flow chart close  
20 to the month six assessment.

21 I don't know if that's intentional,  
22 but they're listed as not having enough  
23 baseline. It looks like they were excluded  
24 because they didn't have enough baseline  
25 episodes, but that wasn't determined until

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1 close to the six-month mark.

2 We have heard a lot of information  
3 about the acute procedural issues -- sorry to  
4 do this again -- relating to electrograms not  
5 being recorded when it was clear to me, it  
6 seems, at least from the way the protocol is  
7 written, that that was an expectation.

8 But there is no comment in any of  
9 the documents about quality assurance measures  
10 that were instituted where a sponsor would say  
11 to the investigators, "Why aren't you  
12 recording it?" because if there is a  
13 deviation, you want to figure out why that is  
14 happening, especially if the deviation becomes  
15 so consistent.

16 So I guess, in essence, what I am  
17 saying is to the sponsor, how can I be  
18 reassured that the data were collected not  
19 only according to the protocol, which has  
20 already been questioned by the way the FDA has  
21 described and I have read the way the protocol  
22 is written about electrograms, et cetera, in  
23 the procedure but also the way the data were  
24 collected long term in terms of handling the  
25 strips and the core labs and changing core

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1 labs in the middle and did those core labs  
2 look at all patients paired, et cetera?

3 DR. CHER: I apologize up front,  
4 but the answer is going to be long-winded  
5 because you have raised several issues. With  
6 respect to electrogram measurements, we  
7 actually asked in the phase 3 trial that the  
8 physicians themselves make the measurements  
9 off the screen and record them in case report  
10 forms.

11 With respect to the monitoring lab  
12 that was doing TTM monitoring, you are right.

13 There was a problem with the database. But  
14 at the same time, Cardima employees kept a  
15 shadow database as well as paper recordings of  
16 all the episodes. And we were able to help  
17 the core lab to reconstruct the database. And  
18 I do believe that it is complete.

19 With respect to the flow chart, we  
20 did have some patients who dropped out before  
21 six months. These were patients who moved  
22 away or were otherwise lost to follow-up.  
23 This is something that occurs in all trials,  
24 and this is not preventable.

25 There were a few patients who were

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1 excluded with respect to the effectiveness  
2 analysis because on retrospect look by the  
3 independent cardiologist, he found that the  
4 number of episodes reported by the patient and  
5 recorded, transmitted to the core lab did not  
6 meet the number required for enrollment in the  
7 study. So, in a sense, he disagreed with the  
8 site investigator. And we went with the core  
9 laboratory reading.

10 Finally, with respect to QA  
11 measures, the company went through several  
12 measures to make sure that we kept data, we  
13 monitored sites very carefully, and we did our  
14 best to speak with physicians when data  
15 weren't collected. It is in some cases  
16 difficult to motivate all the physicians to  
17 collect all the data, but we do believe that  
18 we have a data set that is sufficient for  
19 analysis and, moreover, sufficient for  
20 approval.

21 CHAIRPERSON RAMSEY: FDA?

22 DR. ZUCKERMAN: No comment.

23 CHAIRPERSON RAMSEY: Just one  
24 second. I want to make sure I am not  
25 neglecting if there are any questions. Okay.

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1 Please go ahead.

2 MEMBER SACKNER-BERNSTEIN: As a  
3 follow-up, so the independent cardiologist  
4 looking at these strips looked at these strips  
5 only from baseline, looked at all of them?  
6 Was the independent cardiologist blinded?

7 DR. CHER: The independent  
8 cardiologist read strips in a manner that was  
9 not blinded, but they were read in pretty much  
10 a random order. They were read as they came  
11 in in batches.

12 So the physician was highly  
13 unlikely to remember one versus the other.  
14 The independent cardiologist did read and  
15 interpret every single strip that came in.

16 DR. EWING: I do have, I guess, a  
17 question or a clarification. I believe I  
18 heard Dr. Cher say that the protocol was  
19 changed to take out the core lab assessment  
20 without or they told the physicians to measure  
21 the electrograms themselves. And it wasn't  
22 sent to core lab. But that was never changed  
23 in the investigational protocol.

24 DR. CHER: Yes. I would like to  
25 clarify that. Actually, I am going to have to

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1 get back to the panel on this because I  
2 actually don't remember who did the  
3 electrogram measurements. So I will have to  
4 get back to you on that.

5 CHAIRPERSON RAMSEY: Please?

6 MEMBER SACKNER-BERNSTEIN: Thank  
7 you.

8 I just wanted to bring up a topic  
9 to discuss amongst the panel, which has to do  
10 with the manner in which this study was  
11 designed as it's been termed with each patient  
12 used as his/her own control, because I am  
13 concerned when I hear things such as  
14 electrograms or, say, strips from the TTM data  
15 were read in an unblinded fashion, were read  
16 in an unblinded fashion, were read separately  
17 in batches after the fact. When I heard that  
18 the sponsor had a shadow database, so they saw  
19 what the data were all the way through.

20 I don't look at these trials. I  
21 read the description of the regulation as  
22 really fulfilling the external control. I  
23 don't know where the control group is here.  
24 There is no historic database that I can see  
25 presented to the panel by the sponsor or the

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1 FDA that establishes what the comparison group  
2 is.

3 How do people feel about this?  
4 Does this seem to meet the burden for having  
5 some sort of adequate control according to  
6 what we are charged with addressing?

7 MEMBER SLOTWINER: If I can just  
8 comment? It's often very difficult in  
9 electrophysiology to come up with a completely  
10 objective control group. We have a lot of  
11 placebo effect to deal with because most of  
12 our therapies involve either procedures or  
13 implants.

14 So it's quite common that we have  
15 to use the individual patients as their own  
16 control, but I think the only way to draw  
17 meaningful data in that situation is to pay  
18 meticulous attention to the details and to  
19 obtain data objectively and have them  
20 evaluated in a blinded manner and collected at  
21 an objective interval, not one that is  
22 dependent on symptoms or investigator choice.

23 Electrograms, in particular, tend  
24 to fluctuate from beat to beat as the catheter  
25 moves with the respiratory cycle. So there's

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1 a lot of room for interpretation.

2 MS. WHITTINGTON: And the goal is  
3 to be able to take what we learn and use it in  
4 the general population. That's my  
5 frustration. As a consumer, as a patient, how  
6 are you going to give me information that I  
7 can make a decision that this is or is not  
8 with my physician a good decision for me if  
9 the data is random, it's not collected  
10 consistently, and you can't show me trends?

11 CHAIRPERSON RAMSEY: A problem of  
12 not having individual patient pre/post data  
13 bedevils this. I mean, that's my opinion of  
14 this analysis. And we don't have individual  
15 level data to get us out of that problem.

16 MS. WALKER: Wait a minute. We're  
17 talking about the study design and the study  
18 design being flawed, but I think that it's not  
19 the design per se that are the problems that  
20 we are talking about here. It is an execution  
21 of and a data collection. The minimization  
22 bias that occurs within a study can be  
23 mitigated through appropriate measures.

24 And so I think it's less the fact  
25 of can you do a patient's self-control study

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1 and it still be acceptable? I don't think  
2 that's the question. I think the question is,  
3 how do you adequately mitigate any of the bias  
4 that you would introduce by having that study  
5 design?

6 CHAIRPERSON RAMSEY: Are there any  
7 more comments for Jonathan, responses to his  
8 query?

9 DR. CHER: Can I clarify?

10 CHAIRPERSON RAMSEY: We are talking  
11 among ourselves. And then you will have a  
12 chance. Yes.

13 DR. CHER: Thank you.

14 MEMBER SCHMID: I would just make  
15 the comment that a control is basically  
16 supposed to be treated in the study the same  
17 way that the treated individual is. So if  
18 it's two different groups, obviously you want  
19 to keep things as close as possible in the two  
20 groups. And so you want to have things  
21 randomized and so forth.

22 If the patient is serving as their  
23 own control, then obviously you want to make  
24 sure that they have the same possibility for  
25 the endpoint in the control period as they do

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1 in the treatment period. I mean, I think that  
2 is what we are sort of discussing here, is  
3 whether that is the issue.

4 I mean, I would agree. I think the  
5 problem really isn't the design or the  
6 definition of whether the patient can serve as  
7 his or her own control but, rather, were the  
8 appropriate measures available and taken into  
9 account to make sure that the control period  
10 and the treatment period were equal?

11 CHAIRPERSON RAMSEY: Any other  
12 comments from the panel. What I am going to  
13 do I think is -- yes, please?

14 MEMBER BROWNER: To answer your  
15 very specific question, I think one of the  
16 problems that I am struggling with here is  
17 when you have a condition that waxes and  
18 wanes, even though it's sort of omnipresent,  
19 having a pre/post comparison introduces a  
20 whole set of other problems that you wouldn't  
21 get with a chronic condition that was always  
22 there.

23 I think that is part of what I am  
24 struggling with. And, in fact -- is it almost  
25 time for questions again?

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1 CHAIRPERSON RAMSEY: Yes. What I  
2 want to do I think is let FDA and the sponsor  
3 respond very briefly to this conversation, let  
4 Dr. Browner ask a question. And then I want  
5 to move on to the third concern.

6 So I will start with -- actually,  
7 the sponsor seemed most eager to respond. So,  
8 please, if you could respond briefly to our  
9 conversation? Then we will let FDA do the  
10 same, then Dr. Browner's question.

11 DR. CHER: I think that some of the  
12 discussion that I have heard mischaracterizes  
13 the quality of the trial. The patients were  
14 followed closely. And we made our best  
15 attempts to make sure that they were  
16 compliant.

17 We had a large number of symptom  
18 recordings that were evaluated fairly. The  
19 cardiologist who was looking at all of the  
20 strips looked at them in batch mode, perhaps a  
21 month after they were collected, but they were  
22 collected in real time from patients who were  
23 using an objective device to collect their  
24 symptom recordings.

25 I think the results of the trial

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1 are internally consistent. They're also  
2 externally consistent and consistent with the  
3 literature.

4 With respect to Dr. Browner's  
5 comment on pre/post variation, you heard  
6 modeling that was presented by both me and Dr.  
7 Li to suggest that the success rate due to  
8 random chance alone would be fairly low and  
9 not close to what we observed.

10 Finally, the natural history of  
11 paroxysmal atrial fibrillation in contrast to  
12 what we are hearing just now is actually  
13 well-understood. I presented to you some data  
14 on recordings from patients with pacemakers  
15 during a four-month period. There was a  
16 before and an after period. And we showed  
17 that there was on average an equal number of  
18 episodes before and after.

19 Dr. Saksena also would like to  
20 comment on natural history.

21 CHAIRPERSON RAMSEY: I'm going to  
22 turn it over to FDA because I do want to move  
23 things along if you have a comment.

24 DR. ZUCKERMAN: Okay. The agency  
25 has just heard a very rich discussion about

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1 the problems of the conduct of this trial. We  
2 are in agreement. And, again, these are the  
3 problems that we have struggled with for the  
4 last four years.

5           Again, Dr. Cher has made some  
6 comments about how the modeling "proves" that  
7 regression to the mean and other factors can  
8 be minimized. The agency disagrees with that  
9 statement. We will be more than happy to have  
10 our statistical group bring you through a full  
11 presentation, but in the end, again, it goes  
12 back to the fact that I think we will all have  
13 to conclude at the end of the day we don't  
14 know what are the right assumptions to put in  
15 a model to replace for a clinical trial.

16           And when we don't have data because  
17 of poor conduct in a clinical trial, it's a  
18 major problem that we are unable to resurrect  
19 at the end of the day.

20           CHAIRPERSON RAMSEY: Okay. I want  
21 to turn it back to Dr. Browner, who had a  
22 question.

23           MEMBER BROWNER: My question really  
24 gets to this issue of the condition that waxes  
25 and wanes because I am having a very difficult

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1 time, both with the questions of whether there  
2 is response bias, et cetera, and dealing with  
3 regression to the mean.

4 So my question for the sponsor is  
5 actually quite simple. How many patients were  
6 actually unambiguously cured; that is, they  
7 had no episodes whatsoever from, say, three  
8 months for however long you have been  
9 following them, and of those patients how many  
10 received other treatments besides the  
11 ablation?

12 DR. CHER: I have the answer to the  
13 first question only. There were a total of 29  
14 patients, or 35 percent, who reported no  
15 symptoms during the six months of follow-up.

16 As part of the clinical trial  
17 design, we simply followed those patients  
18 forward in time, 12 months and 24 months, but  
19 did not record symptom episodes. So I don't  
20 have a figure for you in terms of chronic  
21 effectiveness.

22 I can say that in general, the  
23 patients did very well. And there were a  
24 large number of patients who reported the  
25 minimal number of episodes at 12 and 24

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1 months.

2 MEMBER BROWNER: I just want to  
3 clarify. So of those 29 patients, what you  
4 are telling me is that during the 6 months,  
5 they had no episodes but you don't know what  
6 happened to them thereafter? And of those 29,  
7 how many had received some of these other  
8 somewhat disputed therapies?

9 DR. CHER: I don't have the answers  
10 to those questions.

11 DR. EWING: In terms of the  
12 question of cure, in fairness to Cardima, they  
13 don't want to indicate their device to cure  
14 AF. It's a palliative treatment.

15 And when we think about the atrial  
16 fibrillation waxing and paroxysmal atrial  
17 fibrillation waxing and waning, Dr. Cher has  
18 presented results of pacemaker surveillance.  
19 And those are episodes of atrial fibrillation,  
20 not necessarily episodes of symptoms.

21 There are multiple articles in the  
22 literature talking about clusters of symptoms.

23 And the clinicians know that it's a  
24 biological system, for one thing, that a  
25 patient's symptoms one month are not going to

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1 be exactly the same as the next month.

2 DR. CHER: Indeed, that may be the  
3 case. I did present some data on clustering,  
4 but it really occurred over the hour to day  
5 period and not over the month period. And I  
6 refer you to the four articles that I  
7 presented.

8 CHAIRPERSON RAMSEY: Okay. Unless  
9 any others have questions on chronic clinical  
10 effectiveness, I want to get to the third  
11 concern raised by FDA, which is that the  
12 risk-benefit profile cannot be assessed. This  
13 is sort of a derivative question.

14 And I kind of want to break it  
15 apart because I want to ask the panel briefly  
16 if they have any questions or concerns about  
17 the safety of the device because that's part  
18 and parcel of risk-benefit before we go to  
19 this general question. Yes?

20 MS. WALKER: I did want to ask a  
21 question because there was a difference in the  
22 way that the agency analyzed or grouped for  
23 the safety analysis versus the way the sponsor  
24 did. The sponsor did a phase 3 and presented  
25 that information. And the safety group that

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1 FDA presented also included some phase 2B. So  
2 I guess I wanted some clarification on  
3 reconciling those two different approaches.

4 CHAIRPERSON RAMSEY: Do you want  
5 someone to start first?

6 MS. WALKER: Please.

7 CHAIRPERSON RAMSEY: Would you  
8 would like to start first?

9 MS. WALKER: Flip a coin.

10 CHAIRPERSON RAMSEY: Okay. Let's  
11 have the FDA start first.

12 DR. EWING: In the interest of  
13 developing a safety profile, we think it is  
14 important to use all of the device use data  
15 that we have. So that's why we combined phase  
16 2B and phase 3.

17 DR. CHER: From my perspective,  
18 there were two adverse events, two serious  
19 adverse events, in the phase 2 trial. And  
20 when we combine them with the five adverse  
21 events in the phase 3 trial, we really get a  
22 picture of safety that doesn't really change.

23 I would also like to point out that  
24 in the phase 3 trial, there was only one that  
25 was device-related.

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1 CHAIRPERSON RAMSEY: Okay.  
2 Jonathan?

3 MEMBER SACKNER-BERNSTEIN: I have  
4 two questions about safety. One has to do  
5 with the hospitalization risk that these  
6 subjects faced post-procedure. I understand  
7 it's always tempting to say that  
8 hospitalizations relate or don't relate or may  
9 relate or may not relate to a study  
10 intervention, but I would like to put that  
11 aside for a minute.

12 I notice that there are two  
13 different sources of data on hospital visits  
14 that give somewhat different numbers, it seems  
15 to me, one from the Cardima pack page 0065 and  
16 one from the FDA pack volume 2, section 18,  
17 page 162.

18 If we just look within the first  
19 six months, for example, Cardima talks about  
20 five ER visits and ten hospitalizations. I  
21 think that they are talking about these being  
22 arrhythmic risks. And the FDA talks about a  
23 total of 14 hospitalizations, which they  
24 specifically state are due to cardiac  
25 arrhythmias.

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1           Whichever number you want to choose  
2           -- and I'll ask each to use their own numbers  
3           -- what would, therefore, be the confidence  
4           intervals around the risk of hospitalization?

5           We can start with just arrhythmic risk,  
6           arrhythmic cause of hospitalization over the  
7           first six months.

8           DR. CHER:    Pardon me while I look  
9           it up in the PMA that was submitted.

10          MEMBER SACKNER-BERNSTEIN:   Yes.    I  
11          can go over those pages again.   Did you catch  
12          where I'm talking about?

13          DR. CHER:    No.    Actually, I did  
14          not.

15          MEMBER SACKNER-BERNSTEIN:    Okay.  
16          So Cardima, it's listed in the stamped pages  
17          in the bottom as page 0065.   There's also on  
18          the page in the Cardima thing, it's page 45 of  
19          that particular batch of pages.   And the FDA  
20          was in pack 2 -- volume 2, section 18, the  
21          tables on page 162.

22          DR. KOCHERIL:   Let me just make a  
23          general comment that in order to interpret  
24          that, you would have to go back six months and  
25          see how often these patients were showing up

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1 in emergency rooms or getting hospitalized for  
2 atrial fibrillation because you don't really  
3 know that that was in any way related to the  
4 procedure.

5 I mean, I have my own patients.  
6 Some are very stoic and don't come in for  
7 atrial fibrillation. Even when they are  
8 advised by a nurse to come in, they will wait  
9 until I show up in the office the next day and  
10 call me directly. And there are others who  
11 will show up in the ER with PACs. So it's a  
12 little bit hard to interpret.

13 DR. CHER: I would actually like to  
14 refer the panel to the data that we submitted  
15 in the 2004 PMA amendment in which there were  
16 34 hospitalizations in follow-up in 21  
17 subjects, of which 30 were specifically for  
18 arrhythmia and 25 were AF. I think altogether  
19 that presents a picture of a reasonable  
20 hospitalization rate.

21 I can't comment right now on the  
22 table that you referred to. Yes, this is the  
23 table that was submitted in the PMA amendment.

24 And, again, I would like to ask the  
25 electrophysiologist on the panel to put this

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1 into perspective and to give us a comment as  
2 to whether he thinks this is a high  
3 hospitalization rate for patients with --

4 CHAIRPERSON RAMSEY: You can't ask  
5 the panel questions.

6 DR. CHER: Okay.

7 CHAIRPERSON RAMSEY: Sorry. You  
8 can comment on that. And that would be  
9 perfectly appropriate.

10 DR. CHER: I apologize.

11 MEMBER SACKNER-BERNSTEIN: The  
12 second part of my question about risk has to  
13 do with the logistics of how the procedure was  
14 done. It looks from the data submitted that  
15 out of 111 procedures that are listed -- and I  
16 imagine this was from the pre-amendment 6  
17 submission, where it's 2B and 3 data together  
18 -- that out of the 111 procedures that were  
19 performed, 43 of them -- that's 38.7 percent  
20 -- required general anaesthesia and  
21 intubation.

22 So it seems to me that when a  
23 procedure is being described, as it has been,  
24 as being the relatively straightforward one,  
25 where electrophysiologists who are not the

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1 world's experts are going to be able to handle  
2 this catheter fine, that there is obviously  
3 something else to this procedure besides just  
4 a catheter that can be handled by a relatively  
5 novice electrophysiologist without a big deal  
6 with almost 39 percent of people require  
7 general anesthesia and intubation during a  
8 procedure.

9 DR. KOCHERIL: There is going to be  
10 a lot of site-to-site variability in AF  
11 ablation procedures in general. I could tell  
12 you at my site there was no use of general  
13 anesthesia at all. These were all conscious  
14 sedation procedures.

15 There are some investigators -- and  
16 you will see this in the PVI literature as  
17 well where every PVI is a general anesthesia  
18 case. And that is an issue of keeping the  
19 patient absolutely still to minimize  
20 complications. But that is certainly not a  
21 requirement for doing this procedure. You  
22 don't need general anesthesia.

23 DR. SAKSENA: Perhaps I can also  
24 add to that. At our place, we have nine  
25 electrophysiologists performing these

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1 procedures. We probably have about six or  
2 eight anesthesiologists who go through the lab  
3 to cover it. And I would say it's a 50/50  
4 split that half the anesthesiologists decide  
5 that they would prefer to give general  
6 anesthesia, and the other half don't.

7 I can tell you the three hospitals  
8 we do ablation at, at one hospital, we have  
9 never intubated a patient for AF ablation.  
10 And then at the other hospital, some of the  
11 anesthesiologists do.

12 CHAIRPERSON RAMSEY: Did you have a  
13 comment or a question?

14 MEMBER SLOTWINER: Yes. My  
15 experience, Jonathan, is that there is a high  
16 degree of variability amongst  
17 anesthesiologists as to what they prefer as  
18 well as electrophysiologists. And fairly deep  
19 conscious sedation versus intubation, it's not  
20 that big a difference. And I'm not sure that  
21 is of terribly important significance to the  
22 study.

23 CHAIRPERSON RAMSEY: Any other  
24 questions on safety per se? Oh, okay. I'm  
25 sorry. Did you want to have a moment to

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1 respond?

2 DR. EWING: Yes. I have a comment  
3 about the hospital visits question. It's  
4 important to remember here that 30 patients  
5 were seen in 24. There was follow-up on 30  
6 patients at 24 months and 64 at 12. So that's  
7 the denominator for that table.

8 CHAIRPERSON RAMSEY: Thank you.  
9 Okay.

10 DR. CAMPBELL: I am Greg Campbell.  
11 I am the Director of Biostatistics in CDRH.

12 And, Dr. Sackner-Bernstein, I think  
13 you asked about a confidence interval for  
14 hospitalizations. If there are 18 patients  
15 out of 84 who are hospitalized for afib or  
16 atrial flutter, that works out to an  
17 approximate confidence interval of 18 percent  
18 plus or minus 8 percent. So that's for the  
19 six-month time period.

20 CHAIRPERSON RAMSEY: Ms. Walker,  
21 did you have a question? No?

22 Any more questions or comments on  
23 safety? I'm going to try to move this to a  
24 close. I want to sort of get to this sort of  
25 general issue of risk-benefit profile cannot

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1 be assessed. I consider that sort of an FDA  
2 assessment and based on, really, the first two  
3 issues combined with what their assessment of  
4 safety is.

5 But if anyone on the panel would  
6 like to comment or have a question on that  
7 concern three, then we should do it now. Yes?

8 MEMBER SLOTWINER: Maybe I can make  
9 just one more comment. Regarding the  
10 pacemakers as a complication, I think it is  
11 really difficult to say whether that was a  
12 complication. I guess it was a prespecified  
13 maybe -- I'm not positive -- prespecified  
14 problem for the protocol, but these patients  
15 do have a very high incidence of going on to  
16 need a permanent pacemaker.

17 MEMBER SACKNER-BERNSTEIN: In terms  
18 of the risk-benefit ratio, how does the rest  
19 of the panel feel about one of the  
20 publications that addresses this specifically  
21 and some others that allude to the fact that  
22 after these procedures, there are patients  
23 whose atrial fibrillation could be interpreted  
24 as shifting from symptomatic to asymptomatic  
25 in terms of essentially a response just to the

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1 fact that there is a procedure that one could  
2 interpret those data says changes perception  
3 of the atrial fibrillation? How important is  
4 that in deciding the potential benefit?

5 CHAIRPERSON RAMSEY: So are you  
6 asking if there is a placebo effect?

7 MEMBER SACKNER-BERNSTEIN:  
8 Essentially, yes.

9 CHAIRPERSON RAMSEY: Yes.

10 MEMBER SLOTWINER: Well, I think it  
11 is very important. And that's why an  
12 objective assessment of success is so  
13 important in a study where patients serve as  
14 their own controls.

15 And placebo effect is helpful  
16 sometimes. We're happy with it. But for  
17 purposes of approval, I think, you know, you  
18 need higher evidence.

19 CHAIRPERSON RAMSEY: Any other  
20 comments from the panel on Jonathan's  
21 opposition?

22 (No response.)

23 CHAIRPERSON RAMSEY: I sense that  
24 it is time for a break. And we will take a  
25 15-minute break. And then when we return, we

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1 will have a chance for the summaries, ten  
2 minutes, from the FDA and Cardima. So let's  
3 try to return as close to 4:00 o'clock as  
4 possible. Thank you.

5 (Whereupon, the foregoing matter  
6 went off the record at 3:50 p.m. and went back  
7 on the record at 4:05 p.m.)

8 CHAIRPERSON RAMSEY: Let's go ahead  
9 and start with the summation. I believe the  
10 order is for FDA to start, followed by  
11 Cardima. So this is a ten-minute summation.  
12 I will give you a warning at five minutes and  
13 one minute.

14 ODE SUMMATION

15 DR. TILLMAN: All right. Good  
16 afternoon. My name, once again, is Donna B.  
17 Tillman. And I am the Director of FDA's  
18 Office of Device Evaluation. I am here to  
19 offer a few final and brief remarks about  
20 FDA's review of the Cardima revelation Tx with  
21 NavAblator system and why I believe that  
22 Cardima has not provided sufficient valid  
23 scientific evidence to support approval of the  
24 system.

25 As you know, FDA's mission is to

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1 protect the public health by making sure that  
2 medical devices are safe and effective while  
3 at the same time promoting public health by  
4 ensuring ready access to important new  
5 technologies.

6 It's not sufficient for there to be  
7 a clinical need for a new therapeutic  
8 approach. Indeed, there must be more than  
9 just a need. There must also be data. There  
10 must be valid scientific evidence to show that  
11 a specific device is safe and effective for a  
12 particular intended use, not simply that there  
13 is a need in the clinical community for the  
14 device.

15 So to determine that Cardima has  
16 demonstrated a reasonable assurance of  
17 effectiveness, you must find that in a  
18 significant portion of the target population,  
19 the device will provide clinically significant  
20 results. I think those are the two key  
21 points: significant portion of the target  
22 population and clinically significant results.

23 As discussed by the members of the  
24 FDA review team, the results of the primary  
25 endpoint analysis are not interpretable due to

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1 reporting issues for the chronic endpoint as  
2 well as the lack of data for the acute  
3 procedural endpoint.

4 To determine that Cardima has  
5 demonstrated a reasonable assurance of safety,  
6 you must find that the probable benefits to  
7 health outweigh any probable risks and that  
8 the device does not present an unreasonable  
9 risk of illness or injury.

10 As we are unable to determine the  
11 true safety profile for the revelation Tx  
12 system due to lack of data regarding how the  
13 device was used during the study, it cannot be  
14 determined if the safety of the system  
15 outweighs the equally uncertain benefits  
16 provided.

17 In recognition of the original  
18 clinical data set, Cardima has attempted to  
19 provide additional data and analyses from the  
20 same problematic clinical trial. These data  
21 and analyses do not resolve the underlying  
22 issues with the trial conduct that were first  
23 raised at the May 2003 Circulatory Devices  
24 Advisory Panel and in FDA's first and second  
25 "not approvable" letters.

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1 Additional prospective data are  
2 necessary to demonstrate that the device is  
3 safe and effective for its intended use in the  
4 paroxysmal AF patient population. Due to the  
5 significant issues regarding safety and  
6 effectiveness that still remain, we believe  
7 that these data must be collected and  
8 evaluated in the pre-market setting.

9 Today you also heard some  
10 discussion about the review process. The  
11 recommendations that you make should be based  
12 on a careful analysis of the clinical data  
13 presented before you today.

14 Although the FDA review team does  
15 not believe that Cardima has presented  
16 sufficient data to demonstrate a reasonable  
17 assurance of safety and efficacy at this time,  
18 we continue to be willing to work with the  
19 company to develop additional clinical data  
20 that would be necessary to provide the  
21 appropriate evaluation of the system.

22 Thank you for your time and your  
23 consideration.

24 CHAIRPERSON RAMSEY: Well, thank  
25 you. That was very brief.

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1 No other comments from FDA?

2 (No response.)

3 CHAIRPERSON RAMSEY: Okay. Then we  
4 will turn it over to Cardima, who also has ten  
5 minutes to summarize their arguments. And,  
6 again, I will alert you when five minutes are  
7 left and then when one minute is left.

8 CARDIMA SUMMATION

9 DR. CHER: We prepared some slides.

10 May I have the slides, please? Thank you  
11 very much. My name is Daniel Cher. I'm  
12 former Medical Director at Cardima. I  
13 appreciate the opportunity we have to address  
14 the panel today about this issue.

15 Here I put the proposed indication  
16 statement that the Revelation Tx microcatheter  
17 system is indicated for the symptomatic  
18 treatment of drug-refractory paroxysmal atrial  
19 fibrillation by creating continuous RF  
20 ablation lesions in the right atrium.

21 I believe that the study design  
22 that we put together conforms well with  
23 regulations and with guidance subsequently put  
24 forth by FDA. In contrast to what you heard,  
25 the study was well-controlled with each

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1 patient serving as his own control. And that  
2 type of control is a valid type of control.

3 The analyses that we have done  
4 confirm that the placebo effect cannot explain  
5 the outcomes that we observed. The primary  
6 endpoint was met in a significant proportion  
7 of the population. And I remind you that the  
8 primary endpoint required a significant  
9 reduction in symptomatic AF episodes.

10 Secondary endpoints were  
11 significant and clinically meaningful. And  
12 they provided good support for the primary  
13 effectiveness analysis. The safety profile  
14 that we have discussed with a five percent  
15 serious adverse event rate for this patient  
16 population with this disease is one that's  
17 clinically reasonable.

18 We have come to a decision point as  
19 to whether the benefits outweigh the risks.  
20 And I believe that the data that we have  
21 presented allow you to come to that same  
22 conclusion. The results that we have shown  
23 are internally consistent. And they are  
24 consistent with the surgical and other  
25 ablation literature.

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1                   Let's turn first to acute  
2 procedural effectiveness. I believe that this  
3 was demonstrated. We provided data and  
4 analyses to demonstrate amplitude reduction,  
5 which is an accepted, an adequate procedure  
6 endpoint. It's a procedure endpoint that's  
7 still used today in linear ablations in atrial  
8 fibrillation. I think it is unrealistic to  
9 expect a demonstration of amplitude reduction  
10 at each electrode. And I remind you of the  
11 long discussion that we had wherein we  
12 discussed why that cannot occur in all cases.

13                   The investigators did follow the  
14 protocol to create the lines. That combined  
15 with the instructions for use, which are  
16 really quite simple, allow us to be certain  
17 that the physicians actually did create the  
18 lesions that they intended to create.

19                   Let's talk about chronic  
20 effectiveness. I believe that the study  
21 demonstrated chronic clinical effectiveness in  
22 our patient population. The study was  
23 designed per the recommendations of an expert  
24 panel. It was a well-conducted study with  
25 each patient serving as his own control.

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1 These were highly symptomatic patients who  
2 were highly drug-refractory.

3 In this patient population, the  
4 natural history of the disease is very  
5 well-understood. These patients do not get  
6 better on their own. And, for that reason, a  
7 control group is not necessary.

8 We had independent verification of  
9 all trans-telephonic monitoring transmissions  
10 by a cardiologist. In addition, the study  
11 sites underwent auditing by FDA. This is one  
12 of the largest multi-center clinical trials  
13 that's available for atrial fibrillation.

14 We had a high success rate with 58  
15 percent of patients meeting the threshold for  
16 success. And, as I said before, in this  
17 patient population, which was drug-refractory  
18 and with a long history of paroxysmal atrial  
19 fibrillation, there is no expectation of  
20 improvement in this group. Quality of life  
21 data correlated very nicely with symptomatic  
22 reduction in episodes, providing support for  
23 chronic effectiveness.

24 With respect to the risk-benefit  
25 assessment, I believe that it's favorable.

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1 The risk of this device and the way that it is  
2 used is low. It is a minimally invasive  
3 device. We observed no deaths, strokes, or  
4 frantic nerve injury. There was one pacemaker  
5 placed for inadvertent sinus node ablation.

6 Overall I think the safety profile  
7 of this device is excellent and is adequate  
8 for the panel to consider. Weighing against  
9 the risks are the high benefit. We observed  
10 clinically meaningful improvements in  
11 symptomatic AF episodes and quality of life in  
12 patients with a very low expectation of  
13 spontaneous success.

14 I believe that right atrium  
15 ablation is important as a treatment strategy  
16 and should be available to physicians to use  
17 to treat atrial fibrillation.

18 In conclusion, we believe that we  
19 have brought substantial valid scientific  
20 information that meets regulatory criteria.  
21 The study acute endpoint is valid and is  
22 currently recognized as a valid catheter  
23 ablation procedure endpoint. A large amount  
24 of data were brought to show that this  
25 procedure endpoint was collected in a wide

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1 number of centers.

2 The chronic clinical effectiveness  
3 was also demonstrated by a significant  
4 reduction in symptomatic AF episodes. And  
5 these data are supported by quality of life  
6 and long-term data. I think the risk-benefit  
7 ratio has been determined and I think is very  
8 reasonable.

9 I would like to now let the panel  
10 know that we at Cardima have heard what you  
11 have said. And we have specifically heard  
12 your concern regarding the acute procedural  
13 endpoint.

14 We believe and I think that the  
15 panel could consider that the acute procedural  
16 endpoint could be addressed in a small study  
17 in which we use EnSite technology, a mapping  
18 technology that you have seen presented today,  
19 in order to confirm that block does occur and  
20 ablation does occur in the patients who  
21 receive our procedure. And I would like the  
22 panel to give that some consideration.

23 I would like to request that the  
24 panel make an approvable decision, perhaps  
25 with this condition. Thank you very much.

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1 CHAIRPERSON RAMSEY: Thank you for  
2 your summation. We are now going to turn to  
3 the panel deliberation and vote phase of this  
4 meeting. Before we get to that, the voting  
5 members' deliberation and vote, I would like  
6 to ask the industry representative and the  
7 consumer representative if they have any  
8 comments that they would like to share with  
9 the panel before we take our vote. And you  
10 are welcome to make comments or not to as you  
11 see fit.

12 Let's start with consumer first.  
13 I'm sorry. No direction there.

14 (Laughter.)

15 PANEL DELIBERATION AND VOTE

16 MS. WHITTINGTON: My concerns are  
17 with the lack of the early endpoint data and  
18 correlation of that to long-term benefits. I  
19 also have questions about the chronic  
20 effectiveness of this procedure because I  
21 haven't seen a lot of data that shows me that  
22 that it is proven effective over a long period  
23 of time.

24 I think in correlation with medical  
25 treatment, it looks like it probably is, but

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1 this by itself certainly isn't. And I don't  
2 think that they purport it to be, that it's in  
3 combination with some medical indication  
4 treatment.

5 I'm concerned, too, that potential  
6 patients who are going to receive this  
7 treatment have the information put in front of  
8 them so that they clearly understand that this  
9 may not stop the need for other types of  
10 treatment and may not be instead of the need  
11 for pacemaker implantation to manage this  
12 disease.

13 We haven't talked about any of the  
14 information that they are giving patients in  
15 this because we have really focused on the  
16 basic research, but I think that needs to be  
17 said at this point so that we're sure that  
18 anyone who is going to receive this treatment  
19 understands that it's 58 percent, not 88  
20 percent, effective and what other treatments  
21 or concomitant treatments that the patient may  
22 need to have in order to manage their disease  
23 process.

24 CHAIRPERSON RAMSEY: Thank you very  
25 much for that comment.

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1           Now I'll turn it to our industry  
2 representative and let her make a comment.  
3 Thank you.

4           MS. WALKER:    Okay.    I thank the  
5 sponsor and the agency as well for all the  
6 presentations.    It was very informative.    It  
7 was a lot of information.    It is a very  
8 important topic.    Atrial fibrillation is  
9 indeed a large focus for a lot of people in  
10 this industry and in the health care industry.  
11        So I appreciate that.

12           I would like the panel to consider  
13 as they go into deliberation a couple of  
14 things.    One is an assessment of what is it  
15 that we do think that we know from this study,  
16 what does this study tell us, and is there a  
17 modification to the use, to the intended use,  
18 or indications that the panel could suggest?

19           Perhaps as this procedure as an  
20 adjunctive therapy in conjunction with  
21 additional drugs or continued dosing, that's  
22 just a wild suggestion for you to think about  
23 or some other modification of the intended use  
24 that would allow a post-market study to answer  
25 the final questions that are associated with

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1 this. Just it's something that I would ask  
2 that you consider.

3 And also consider the time frame  
4 and how much we have learned now from when  
5 this study was actually initiated. We know a  
6 lot more now about atrial fibrillation, about  
7 atrial flutter, about a lot of the  
8 technologies -- the visualization technologies  
9 that we have today are much better than they  
10 were -- and take those, the availability of  
11 those things, into consideration as well.

12 CHAIRPERSON RAMSEY: Thank you very  
13 much.

14 Okay. So in your packets you all  
15 have a diagram outlining the voting procedure.

16 And I would ask that you have that in front  
17 of you to guide us through the voting process.

18 Dr. Braier is now going to read the  
19 panel recommendation options for pre-market  
20 approval applications. Dr. Braier?

21 EXECUTIVE SECRETARY COLLAZO-BRAIER:

22 "The medical device amendments to the Federal  
23 Food, Drug, and Cosmetic Act, the Act, as  
24 amended by the Safe Medical Devices Act of  
25 1990, allows the Food and Drug Administration

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1 to obtain a recommendation for an expert  
2 advisory panel on designated medical device,  
3 pre-market applications, PMAs, that are filed  
4 with the agency.

5 "The PMA must stand on its own  
6 merits. And your recommendation must be  
7 supported by safety and effectiveness data in  
8 the application or by applicable publicly  
9 available information.

10 "The definitions of safety,  
11 effectiveness, and valid scientific evidence  
12 are as follows. Safety. This is from 21 CFR  
13 860.7(d)(1). 'There is reasonable assurance  
14 that a device is safe when it can be  
15 determined based upon valid scientific  
16 evidence that the probable benefits to health  
17 from use of the device for its intended uses  
18 and conditions of use when accompanied by  
19 adequate directions and warnings against  
20 unsafe use outweigh the probable risks.'

21 "Effectiveness. 21 CFR  
22 860.7(e)(1). 'There is reasonable assurance  
23 that a device is effective when it can be  
24 determined based upon valid scientific  
25 evidence that in a significant portion of the

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1 target populations, the use of the device for  
2 its intended uses and conditions of use when  
3 accompanied by adequate directions for use and  
4 warnings against unsafe use will provide  
5 clinically significant results.'

6 "Valid scientific evidence. 21 CFR  
7 860.7(c)(2). 'Valid scientific evidence is  
8 evidence from well-controlled investigations,  
9 partially controlled studies, studies and  
10 objective trials with a matched control,  
11 well-documented case histories conducted by  
12 qualified experts, and reports of significant  
13 human experience with a marketed device from  
14 which it can be fairly and responsibly  
15 concluded by qualified experts that there is  
16 reasonable assurance of the safety and  
17 effectiveness of a device under its conditions  
18 of use.'

19 "Isolated case reports, random  
20 experience, reports lacking in sufficient  
21 details to merit scientific evaluation, and  
22 unsubstantiated opinions are not regarded as  
23 valid scientific evidence to show safety or  
24 effectiveness.

25 "Your recommendations for vote are

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1 as follows: approvable if there are no  
2 conditions attached, approvable with  
3 conditions. The panel may recommend that the  
4 PMA be found approvable subject to specific  
5 conditions, such as physician or patient  
6 education, labeling changes, or a further  
7 analysis of existing data. Prior to voting,  
8 all of the conditions should be discussed by  
9 the panel.

10 "Not approvable. The panel may  
11 recommend that the PMA is not approvable if  
12 the data do not provide a reasonable assurance  
13 that the device is safe or the data do not  
14 provide a reasonable assurance that the device  
15 is effective under the conditions of use  
16 prescribed, recommended, or suggested in the  
17 proposed labeling.

18 "Following the voting, the Chair  
19 will ask each panel member to present a brief  
20 statement outlining the reasons for his or her  
21 vote."

22 CHAIRPERSON RAMSEY: Thank you, Dr.  
23 Braier.

24 So now I will be asking for a main  
25 motion. So is there a main motion to

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1 recommend approval, approvable with  
2 conditions, or not approvable from the panel?

3 Somebody has to. Dr. Sackner-Bernstein?

4 MEMBER SACKNER-BERNSTEIN: Well, I  
5 know I am just supposed to make a motion, but  
6 I can't help myself from saying something  
7 first. I think that when this study was  
8 performed, what we have learned is that there  
9 is a tremendous amount of information that can  
10 be gained by performing multi-center trials.  
11 But there is also a lot of difficulty when you  
12 are the first one to attempt to do something.

13 There was very little laid out in terms of  
14 what the requirements would be, what the  
15 expectations would be.

16 And I think that there is a lot of  
17 credit to be given to the sponsor for  
18 venturing into this area, where there is such  
19 an important public health problem, where the  
20 rules really weren't as well-established as  
21 they probably would have liked when they got  
22 started.

23 But, with that said, having read  
24 the regulations that Nancy just read that talk  
25 about safety and effectiveness that we need to

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1 see, the regulations include the need to be  
2 able to write instructions that assure that  
3 when a device is used in clinical practice,  
4 that users know how to use it so that there's  
5 a reasonable assurance of safety and that  
6 there is a reasonable assurance that there  
7 isn't unsafe associated effects.

8 So, with that said, the way the  
9 regulations are written, even though I would  
10 like to have more opportunities for physicians  
11 to treat patients with atrial fibrillation, I  
12 am going to make a motion that this  
13 application be not approvable.

14 CHAIRPERSON RAMSEY: Thank you.

15 Is there a second for that motion?

16 MEMBER HIRSHFELD: Second.

17 CHAIRPERSON RAMSEY: Second? Okay.

18 Now, Dr. Sackner-Bernstein, being such an  
19 expert on the panel, has already made  
20 discussion on the motion, which was an  
21 excellent example for the rest of us. But I  
22 would like to ask if there are others who  
23 would like to have discussion on the motion  
24 before we move to voting. Yes?

25 MEMBER SCHMID: I'm still puzzled

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1 by whether there is a chance from the data  
2 that are available for any more information to  
3 be gained. I have listened to both sides.  
4 And I know that there is obviously a  
5 disconnect here between their beliefs about  
6 what the data tell them.

7 On the other hand, I haven't all  
8 day been thinking that both sides have been  
9 looking at the same data. It appears to me as  
10 if the sponsor is saying that, for example, in  
11 the acute data, that there are indications  
12 that the line of block was achieved.

13 When we pressed for data on that,  
14 we were told that there were measurements  
15 available. The agency has said that such data  
16 were not presented to them and that basically  
17 there's not enough information available to be  
18 able to make a call. I agree with you. I  
19 haven't seen any such data, but I am still  
20 wondering if such data are available and  
21 whether it could be looked at.

22 Now, it may very well be that this  
23 has been discussed ad nauseam over the last  
24 three years, but I still kind of wonder from a  
25 mediation standpoint if there is a possibility

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1 of any kind of resolution to be gained here.  
2 And that's really what I am struggling with.

3 CHAIRPERSON RAMSEY: Any further  
4 discussion?

5 MEMBER SLOTWINER: And as an  
6 electrophysiologist, there are a lot of  
7 aspects of this technology that are very  
8 attractive. And it may be quite effective,  
9 but from the information that I have seen  
10 represented, I wouldn't know how to use it in  
11 the electrophysiology laboratory without  
12 additional equipment. And I don't think that  
13 is what is being asked of us.

14 CHAIRPERSON RAMSEY: Please?

15 MEMBER HIRSHFELD: Since I seconded  
16 the motion, let me make a couple of comments  
17 about my rationale. I think there are two  
18 questions. The first is the question of what  
19 is the value of the concept of right atrial  
20 ablation, either as a stand-alone procedure,  
21 which is the way that it was studied in this  
22 protocol, or, as was hinted at by some of the  
23 sponsors' representatives as a potential  
24 adjunct to left atrial pulmonary vein  
25 isolation, which was not studied in this

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1 protocol. And I think that is a very  
2 tantalizing clinical question for all of us  
3 who take care of cardiovascular patients.

4 The second question is, how well  
5 does the sponsor's data support the efficacy  
6 of its system in treating paroxysmal atrial  
7 fibrillation? I think those are the two  
8 questions that are in front of us, the second  
9 one being the regulatory question, the first  
10 one being the clinical question that we would  
11 all like the answer to.

12 In looking at everything that was  
13 presented today, I come away with the visceral  
14 feeling that there is a signal in this data  
15 that this probably was beneficial to some  
16 patients who received this treatment, but my  
17 problem is that I don't know who they are. I  
18 don't know how to identify them preemptively.

19 I am not sure how many there are.

20 So, therefore, I think it's partly  
21 that we're really uncertain as to what the  
22 actual degree of acute procedural success was.

23 We're uncertain as to what the degree in  
24 magnitude of the chronic benefit was.

25 And so, as a result, if this device

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1 were available, I think we would be uncertain  
2 as to how to select patients who were  
3 candidates for the procedure.

4 CHAIRPERSON RAMSEY: Good comment.  
5 Any other comments?

6 (No response.)

7 CHAIRPERSON RAMSEY: If there are  
8 none, -- it looks like there are none -- I  
9 will say that it has been moved and seconded  
10 that the Cardima, Inc. PMA P020039 for the  
11 Revelation Tx microcatheter ablation system is  
12 not approvable.

13 I will need individual votes. And  
14 so we will go around the table. And I would  
15 ask that you state your name for the record  
16 and whether you vote yes or no or abstain are  
17 the three choices. So I will start with Dr.  
18 Schmid.

19 MEMBER HIRSHFELD: Could you just  
20 clarify what yes means and what no means?

21 CHAIRPERSON RAMSEY: Oh, yes. Yes  
22 is that you agree that it is not approvable.  
23 Okay? If you say no, then we go back and  
24 entertain another motion. So yes means not  
25 approvable.

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1                   MEMBER SCHMID:   Okay.   My name is  
2 Christopher Schmid.   My vote is that yes, it  
3 is not approvable.   My reasons for this are  
4 that my colleagues on the panel as  
5 cardiologists did not see that the data are  
6 sufficient to permit them to use this device.  
7     They are not sure of its efficacy.

8                   I have not seen any data which  
9 would indicate to me that this device has  
10 proven efficacy.   And in the absence of such  
11 data, I believe that the regulations require  
12 that it not be approved.

13                  CHAIRPERSON RAMSEY:       Now, you  
14 actually skipped ahead to your reasons, and  
15 that was very nice because we don't have to go  
16 to you next time.   But I will ask everyone  
17 just to vote yes, no, or abstain.   And then we  
18 will go to the rationale section.   Dr.  
19 Hirshfeld?

20                  MEMBER HIRSHFELD:   My name is John  
21 Hirshfeld.   And I am voting yes.

22                  MEMBER SLOTWINER:   My name is David  
23 Slotwiner.   And I am voting yes.

24                  CHAIRPERSON RAMSEY:   Dr. Browner?

25                  MEMBER BROWNER:   My name is Warren

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1 Browner. And I am voting yes.

2 MEMBER SACKNER-BERNSTEIN: Jonathan  
3 Sackner-Bernstein. I am voting yes.

4 CHAIRPERSON RAMSEY: Thank you all.  
5 And I will take Dr. Schmid's response as his  
6 rationale and move on to Dr. Hirshfeld.

7 MEMBER HIRSHFELD: I have nothing  
8 to add to what I said before.

9 CHAIRPERSON RAMSEY: Very good.  
10 Dr. Slotwiner?

11 MEMBER SLOTWINER: Well, I would  
12 like to commend the sponsor on a very  
13 difficult study and a very elegant catheter.  
14 From the perspective of the catheter itself,  
15 it is truly unique in how agile it is. And I  
16 think that the study demonstrated very clearly  
17 in my mind, at least, that it's quite safe.

18 I think part of the reason we're  
19 not able to approve the device is because the  
20 study was started early on in our  
21 understanding of atrial fibrillation. I  
22 really don't know if it's effective at this  
23 point or not, and I hope that we will get to  
24 know that in the future.

25 But I would like to compliment you

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1 on your effort and your time.

2 CHAIRPERSON RAMSEY: Thank you.

3 MEMBER BROWNER: I voted yes  
4 because I am not convinced that there are data  
5 to support the effectiveness of the therapy.

6 CHAIRPERSON RAMSEY:  
7 Sackner-Bernstein?

8 MEMBER SACKNER-BERNSTEIN: I voted  
9 yes, as I stated previously, for those reasons  
10 about the way the regulation requires the  
11 reasonable assurance of safety and efficacy  
12 that I don't think were met.

13 CHAIRPERSON RAMSEY: In this case  
14 the motion has carried five to zero, and there  
15 were no abstentions. Since the panel voted to  
16 recommend that the PMA is not approvable, the  
17 panel is asked to identify what they believe  
18 is needed to make the PMA approvable. And  
19 I'll start again at the right, my right, with  
20 Dr. Schmid.

21 MEMBER SCHMID: I think what we  
22 need to see are some convincing data. And I  
23 would strongly urge the sponsor and the agency  
24 to get together and work out conditions under  
25 which this would be approvable. I think the

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1 agency has been very clear all day that they  
2 are willing to work with the sponsor to do  
3 that.

4 I really believe that such an  
5 attempt is going to have some dividends in  
6 answering this question one way or the other.

7 I think such data can be collected. And I  
8 really hope in the interest of the advancement  
9 of the field, that we can do that.

10 CHAIRPERSON RAMSEY: Yes, Dr.  
11 Hirshfeld?

12 MEMBER HIRSHFELD: I think one of  
13 the things that we heard today is that in  
14 2007, there are better techniques available,  
15 both for acute efficacy assessment as well as  
16 for chronic efficacy assessment, which  
17 probably would provide higher resolution and  
18 more accurate assessment of both of these  
19 things and perhaps offer the possibility of  
20 showing with sufficient statistical power with  
21 a smaller sample size than was originally  
22 designed that this procedure works.

23 And so I would think that a  
24 redesign of the trial using both better acute  
25 and chronic efficacy parameters might very

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1 well demonstrate what the sponsor is trying to  
2 demonstrate.

3 CHAIRPERSON RAMSEY: Thank you.

4 MEMBER SLOTWINER: I think, as my  
5 colleagues have described, what we need is  
6 more evidence, more acute effectiveness,  
7 evidence, and more chronic efficacy data.

8 I don't think that ablation is  
9 likely to be successful if it's isolated to  
10 the right atrium alone, but I do hope that the  
11 sponsor will work with the FDA together to  
12 come up with a protocol to get more data  
13 because I do think that is an area of  
14 tremendous need for our patients.

15 We clearly need better therapies  
16 for atrial fibrillation. And there is  
17 something here. This is a wonderful catheter.

18 And I think studied correctly, studied  
19 differently, with perhaps more objective acute  
20 endpoint success criteria, we could find a use  
21 for it.

22 CHAIRPERSON RAMSEY: Thank you.

23 Dr. Browner?

24 MEMBER BROWNER: I would only add  
25 careful attention to ascertaining what

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1 constitutes success and failure in the chronic  
2 ascertainment and not having wiggle room and  
3 disputed outcomes that make it very difficult  
4 to know whether or not the treatment is  
5 working.

6 CHAIRPERSON RAMSEY: Thank you.

7 Dr. Sackner-Bernstein?

8 MEMBER SACKNER-BERNSTEIN: I  
9 certainly appreciate that the sponsor is  
10 already proposing how to collect more  
11 information because it would be a shame to  
12 have a catheter without a strategy any of the  
13 ways you want to look at this approach to be  
14 one that does not continue to move forward.

15 I think that I would look at the  
16 requirements for such a study to include  
17 things that would go beyond a 15-patient  
18 experience. I think you need to perform the  
19 study in a multi-center fashion so that we  
20 have an understanding about how a catheter  
21 such as this works in the hands of different  
22 investigators, different proceduralists.  
23 There needs to be a way that acute success can  
24 be demonstrated in a fashion that's acceptable  
25 to both.

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1           The outcomes data need to take into  
2 account the fact that there is the potential  
3 for placebo effect so that tracking total afib  
4 burden or some term like that, that would  
5 encompass the total time in atrial  
6 fibrillation.

7           The amount of time spent, whether  
8 it's symptomatic or asymptomatic as well as  
9 symptoms to look at it blinded, there are  
10 certainly recording devices that can  
11 accumulate seven days of continuous hold term  
12 now that weren't available in '98-'99, when  
13 this was being planned. There are some of  
14 those devices that probably have the  
15 capability to be modified to do two weeks at a  
16 time.

17           So you certainly can collect  
18 information on atrial fibrillation in a way  
19 that would be all-encompassing, would minimize  
20 placebo effect, would allow anyone to look at  
21 the data and say this was a blinded  
22 interpretation, this is a set of data that is  
23 internally consistent, that's assessed  
24 multiple time points over the period of  
25 follow-up.

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1           So I would hope that such a study  
2           could be put together so we can see how we can  
3           impact the natural history of this disease.

4           CHAIRPERSON RAMSEY: Thank you. I  
5           would like to thank myself, personally, both  
6           the sponsor and the FDA, for their passion and  
7           their rigor in stating their case. And I  
8           would also very much like to thank my fellow  
9           panel members for all of the effort that they  
10          took in carefully reviewing a very, very large  
11          amount of data.

12          I am now going to ask if Mr.  
13          Weinstein has anything he would like to say  
14          before we adjourn.

15          MR. WEINSTEIN: Yes. Thank you,  
16          Dr. Ramsey.

17          I also want to thank all the panel  
18          members for their diligent work in preparing  
19          for and anticipating in today's meeting. I  
20          especially want to thank you, Dr. Ramsey, for  
21          your leadership as Chair of this panel and for  
22          conducting, as usual, third time now, a very  
23          fair, objective, impartial, and well-balanced  
24          meeting of the Dispute Resolution Panel today.

25          I want to thank Dr. Braier, the

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1 Executive Secretary, of this panel for her  
2 outstanding contributions to the process  
3 before, during, and after these Dispute  
4 Resolution Panel meetings.

5 I want to thank Geretta Wood, the  
6 CDRH panel coordinator, for her wise advice on  
7 the intricacies and potential pitfalls of  
8 planning and coordinating a panel meeting.

9 I would like to thank the Committee  
10 management staff, especially Shirley Meeks and  
11 Ann Marie Williams, for their wonderful  
12 logistical support.

13 And I also want to reiterate my  
14 thanks to the FDA review team and the Cardima  
15 team for all your diligence and hard work in  
16 preparing and participating in today's  
17 meeting. Thank you very much.

18 CHAIRPERSON RAMSEY: Thank you.

19 And now the meeting of the Medical  
20 Devices Dispute Resolution Panel is adjourned.

21 (Whereupon, the foregoing matter  
22 was concluded at 4:42 p.m.)  
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